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Necati Çıtak, Atilla Pekçolaklar

Charlson Comorbidity Index in Predicting Poor Clinical Outcomes and Mortality in Patients with COVID-19
Serap Argun Barış, Haşim Boyacı, Sıla Akhan, Birsen Mutlu, Müge Deniz, İlknur Başyiğit

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ERS International Virtual Congress 2021: Highlights from the Turkish Thoracic Society Early Career Members
Merve Yumrukuz Şenel, Dilek Karadoğan, Ilgım Vardaloğlu, Elif Develi, Selma Çelik, Mina Hızal, Beste Özseren, Aslı Öncel, İlknur Can, Nur Hürsoy, Kübra Uyar, Fatma Gülsüm Karakaş, Berrin Er, Pelin Asfuroğlu, Tuğba Ramaslı Gürsoy, Tuğba Şişmanlar Eyüboğlu, Eylül Pınar Çakır, Dilber Ademhan, Selen Karaoğlanoğlu, Nagehan Emiralioğlu, Nilufer Aylin Acet Öztürk, Feride Marim, Özge Aydın Güçlü, Nazli Çetin, Dilara Ömer Topçu, Pınar Çelik, Metin Akgün

Case Reports

COVID-19 Pneumonia After SARS-CoV-2 Vaccination with CoronaVac: A Case Series from Turkey
Mehmet Meriç Çoban, Mehmet Nuri Yakar, Murat Küçük, Bişar Ergün, Muammer Çelik, Begüm Ergan, Erdem Yaka, Necati Gökmen

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The aim of the journal is to convey scientific developments and to create a dynamic discussion platform about pulmonary diseases. With this intent, the journal accepts articles from all related scientific areas that address adult and pediatric pulmonary diseases, as well as thoracic imaging, environmental and occupational disorders, intensive care, sleep disorders and thoracic surgery. Clinical and research articles, reviews, statements of agreement or disagreement on controversial issues, national and international consensus reports, abstracts and comments of important international articles, interesting case reports, writings related to clinical and practical applications, letters to the editor, and editorials are accepted.

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CONTENTS

Original Articles

89 Six-Week Hospital-Based Pulmonary Rehabilitation in Covid Pneumonia ICU Survivors: Experience from a Tertiary Care Center in Central India
Alkesh Kumar Khurana, Aqeel Hussain, Abhishek Goyal, Sunaina Tejpal Karna, Saurabh Saigal, Raj Krishnan Soman, Mamta Verma, Sagar Khadanga, Gaurav Sahu, Brijendra Singh

97 Altered Cardiac Repolarization in Chronic Obstructive Pulmonary Disease
Fatih Alper Uğuz, Fulsen Bozkuş, Ekrem Aksu, Nurhan Atilla, Hasan Kahraman and Adem Doğaner

104 Obstructive Sleep Apnea Effects on Pulmonary and Respiratory Muscle Function of Obese Children and Adolescents: A Preliminary Study
Sainatee Pratanaphon, Nuntigar Sonsuwan, Siwahdol Chaimano, Sirinad Chandee, Kewalin Autkhruea, Piangkwan Sa-nguanmoo, Khanittha Wonglangka

109 The Impact of Mechanical Ventilation Modes on Complications of Fiberoptic Bronchoscopy in Critically Ill Patients
Murat Küçük, Yasin Levent Uğur, Mehmet Celal Öztürk, Bilgin Cömert, Ali Necati Gökmen, Begüm Ergan

115 Effects of Education on Care Burden and Quality of Life to Caregivers of Patients with COPD
Firdevs Kuzu, Hatice Tel Aydın

123 Is the Thoracic and Back Muscle Mass Associated with Disease Severity in Patients with COVID-19?
Zeynep Aykın Yığman, Ebru Karaca Umay, Galip Aktürk, Mustafa Çağrı Ergün

130 Can Thorax Computed Tomography Severity Score in Coronavirus Disease 2019 Patients Differentiate Smokers from Non-smokers?
Buket Yağcı, Ayse Özlem Balık, Recep Balık, Ulaş Yalım Uncu

137 Is There Any Relationship Between the Number of COVID-19 Tests by Country with the Income Inequality of Countries? A Comparison with Income Inequality Metrics
Necati Çıtak, Atilla Pekçolaklar

145 Charlson Comorbidity Index in Predicting Poor Clinical Outcomes and Mortality in Patients with COVID-19
Serap Argun Barış, Haşim Boyacı, Sıla Akhan, Birsen Mutlu, Müge Deniz, İlknur Başyiğit

Reviews

154 Pulmonary Rehabilitation in Coronavirus Disease 2019 Patients
Ahmet Kıvanç Menekşeoğlu, Dilşad Sindel

162 Turkish Thoracic Society Early Career Members Task Force Group's Virtual Congress Notes: European Respiratory Society International Congress 2020
Deniz Kızılırmak, Dilek Karadoğan, Halime Yıldırım, Fatma Tokgöz Akyıl, Tuğba Şişmanlar Eyüboğlu, Nagehan Emiralioğlu, Ümran Özden Sertçelik, Fatma Esra Günaydın, Özlem Ataoğlu, Merve Sinem Oğuz, Selin Çakmakcı, Neslihan Özçelik, Aslı Öncel, Ali Fırıncıoğluları, Bilge Yılmaz Kara, Dilara Ömer, Selen Karaoğlanoğlu, Nazli Cetin, Fatma Gulsum Karakas, Canan Gunduz Gurkan, Feride Marim, Tuğba Önyılmaz, Demet Polat Yuluğ, Nilufer Aylin Acet Öztürk, Özge Aydın Güçlü, Tuba Çiftçi Küsbeci, İrem Şerifoğlu, Hüseyin Arıkan, Zehra Nur Töreyin, Pınar Çelik, Metin Akgün

173 ERS International Virtual Congress 2021: Highlights from the Turkish Thoracic Society Early Career Members
Merve Yumrukuz Şenel, Dilek Karadoğan, Ilgım Vardaloğlu, Elif Develi, Selma Çelik, Mina Hızal, Beste Özseren, Aslı Öncel, İlknur Can, Nur Hürsoy, Kübra Uyar, Fatma Gülsüm Karakaş, Berrin Er, Pelin Asfuroğlu, Tuğba Ramaslı Gürsoy, Tuğba Şişmanlar Eyüboğlu, Eylül Pınar Çakır, Dilber Ademhan, Selen Karaoğlanoğlu, Nagehan Emiralioğlu, Nilufer Aylin Acet Öztürk, Feride Marim, Özge Aydın Güçlü, Nazli Çetin, Dilara Ömer Topçu, Pınar Çelik, Metin Akgün

Case Reports

185 COVID-19 Pneumonia After SARS-CoV-2 Vaccination with CoronaVac: A Case Series from Turkey
Mehmet Meriç Çoban, Mehmet Nuri Yakar, Murat Küçük, Bişar Ergün, Muammer Çelik, Begüm Ergan, Erdem Yaka, Necati Gökmen

192 Xeroderma Pigmentosum-Associated Childhood Interstitial Lung Disease
Samiksha Kamble, Ketaki Utpat, Unnati Desai, Jyotsna Joshi, Ramesh Bharmal

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Original Article

Six-Week Hospital-Based Pulmonary Rehabilitation in Covid Pneumonia ICU Survivors: Experience from a Tertiary Care Center in Central India

Alkesh Kumar Khurana[1], Aqeel Hussain[1], Abhishek Goyal[1], Sunaina Tejpal Karna[2], Saurabh Saigal[2], Raj Krishnan Soman[1], Mamta Verma[3], Sagar Khadanga[4], Gaurav Sahu[1], Brijendra Singh[5]

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Abstract

OBJECTIVE: There is very limited data on the usefulness of pulmonary rehabilitation in patients with coronavirus pneumonia who have survived intensive care unit care. The primary aim was to explore the feasibility of conducting a pulmonary rehabilitation program in patients with coronavirus disease-19 pneumonia surviving intensive care. The secondary aim was to study the impact of a hospital-based 6-week pulmonary rehabilitation program on exercise capacity, quality of life, and psychological parameters in these patients. This study was conducted at the Center for Pulmonary Rehabilitation, Department of Pulmonary Medicine of the institute.

MATERIAL AND METHODS A total of 27 patients were enrolled. Among them, 14 patients who completed the desired 12 sessions over 6 weeks constituted the pulmonary rehabilitation group and 13 patients who either did not consent or defaulted within the first 2 weeks were considered as controls. Both groups had assessments at 0 and 6 weeks that included a 6-Minute Walk Test, Incremental Shuttle Walk Test, mMRC Dyspnea Scale, Baseline Dyspnea Index, and Transitional Dyspnea Index, Saint George's Respiratory Questionnaire score, and Depression, Anxiety, Stress Scale-21 score.

RESULTS: Significant improvement in dyspnea by mMRC ($P = .01$) and exercise capacity as measured by 6-Minute Walk Test ($P < .001$) and Incremental Shuttle Walk Test ($P = .025$) was seen in the pulmonary rehabilitation group as compared to the control group. There was no significant improvement in quality of life and psychological parameters (Depression, Anxiety, Stress Scale 21 score) after 6 weeks of pulmonary rehabilitation program as measured in our study.

CONCLUSION: Pulmonary rehabilitation is feasible and appears promising in coronavirus disease acute respiratory distress syndrome survivors. However, data from other centers and a larger number of patients are required to imbibe conclusive results.

KEYWORDS: ARDS, COVID, exercise capacity, pulmonary rehabilitation, quality of life
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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) pandemic is the most critical ongoing global health care problem[1] Globally, as of May 19, 2021, there have been 163 869 893 confirmed cases of coronavirus disease-19 (COVID-19), including 3 398 302 deaths, reported to World Health Organization (WHO).[2] The course of COVID-19 infection is variable and unpredictable with most patients experiencing mild illness and spontaneous recovery, but a subgroup of individuals require hospitalization for pneumonia that may vary in severity from mild hypoxemic respiratory failure to acute respiratory distress syndrome (ARDS).[3] The transmission mechanisms and pathophysiology of COVID-19 have been studied extensively, and strategies to prevent the infection and effectively treat the disease have been devised. As a result, different vaccines have been approved within a year of the pandemic for the prevention of COVID-19 infection and its complications. The progress in the understanding of the treatment strategies has culminated in the formulation of effective treatment guidelines by various organizations like WHO, European Respiratory Society, and Surviving Sepsis Campaign Group.[4-6] The most beneficial intervention regarding decreasing mortality has been the use of steroids in appropriate settings.[7] The follow-up of the patients recovering from COVID-19 deserves equal attention as little is known about the sequelae of the COVID-19 and their management.

As we know that COVID-19 shares characteristics with the SARS including angiotensin-converting enzyme-2 (ACE2)-dependent cellular entry and interleukin-6 (IL-6)-driven hyper-inflammation and ARDS,[3] it was anticipated that long-term complications similar to SARS pneumonia could be seen in COVID-19 survivors. The follow-up of SARS survivors months after infection revealed fibrotic features, including airspace opacification and reticular shadowing in up to 36% of the

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patients.[8] A 1-year follow-up study of 97 patients recovering from SARS in Hong Kong showed that 27.8% of survivors had decreased lung function and signs of pulmonary fibrosis.[9] Previous follow-up studies of H1N1-ARDS have revealed that functional impairment persists in some patients even after 6 months of discharge.[10] Anticipating the risk of lung fibrosis in ARDS survivors in general and COVID-related ARDS in particular, different strategies like antifibrotics and pulmonary rehabilitation (PR) have been reviewed in the context of COVID-19.[11]

Previous studies in COVID-19 have shown that some percentage of post-COVID-19 patients had persisting symptoms and lung function impairment along with pulmonary abnormalities more than 100 days after the diagnosis of COVID-19.[12] The relevance of PR in any respiratory disease depends on the long-term sequelae and associated symptoms of the disease. Dyspnea and fatigue are the symptoms that have shown significant improvement with PR in interstitial lung disease.[13] Huang et al[14] recently published results from 6 months of follow-up of a large cohort of more than 1700 patients with COVID-19 from China. The most common residual symptoms at 6 months were fatigue/muscle weakness, anxiety/depression, and sleep disturbances.[14] Hence, they suggested that PR could be helpful in these patients. There is promising literature available regarding the benefit of PR in H1N1 ARDS also as mentioned in a study from Taiwan whereby patients received 2 months PR following H1N1 ARDS and resulted in a normal 6-minute walk distance (6MWD > 80% of predicted value) at 6 months post-discharge.[15] Given the potential benefit PR can have in COVID-19 survivors, guidelines recommend that COVID-19 survivors with a need for rehabilitative interventions at 6-8 weeks following hospital discharge (e.g., multiple treatable traits) should receive a comprehensive rehabilitation program.[16] Extrapolating from the above-mentioned data, we tried to explore the feasibility and effect of PR in the patients of COVID-19 pneumonia with respiratory failure discharged from intensive care unit (ICU) with persistent symptoms.

MATERIALS AND METHODS

In this hospital-based longitudinal study, we enrolled patients of COVID pneumonia with respiratory failure managed in ICU and aimed to study the effect of PR program on outcome parameters such as exercise capacity, level of dyspnea, quality of life (QOL), and mental health status.

MAIN POINTS

- There is hardly any literature about pulmonary rehabilitation (PR) in coronavirus disease (COVID) acute respiratory distress syndrome (ARDS) survivors. To the best of our knowledge, this is the first such paper from the Asian subcontinent.
- A hospital-based PR is very much feasible in COVID ARDS survivors.
- Pulmonary rehabilitation significantly improves the dyspnea index and exercise capacity of such patients as measured by mMRC scale and 6-Minute Walk Test and Incremental Shuttle Walk Test, respectively.

For the assessment of exercise capacity, 6MWD and ISWD were evaluated. The assessment of 6MWD is an established method to evaluate functional exercise capacity in patients with respiratory disease.[17] Also, 6MWD has been shown to be a predictor of survival in patients with chronic respiratory disease, especially COPD.[18] Minimal clinically important difference (MCID) in 6MWD in cardiorespiratory diseases has been described as 54-80 m for cardiorespiratory diseases.[19] Also, ISWT was done alongside, the MCID for which has been reported between 35 and 78 m in different studies.[20,21]

For the assessment of dyspnea severity, mMRC Dyspnea Scale was used, which is a well-known and practiced scale used to stratify dyspnea in patients with chronic respiratory disease.[22,23] We also measured the Baseline Dyspnea Index (BDI) and Transitional Dyspnea Index (TDI), which have been used previously to assess the change in perception of dyspnea before and after rehabilitation. Baseline Dyspnea Index values range from 0 to 12, and the lower the score, the worse is the severity of dyspnea. Transitional Dyspnea Index values range from −9 to+9, and the negative values measure the worsening of dyspnea and the positive value indicates improvement in dyspnea. Minimal important change in TDI has been mentioned as change of ≥1 unit.[24]

Saint George Respiratory Questionnaire (SGRQ) is a disease-specific instrument designed to measure the impact on overall health, daily life, and perceived well-being in patients with obstructive airway disease. It consists of 50 items and 3 domains. These include symptoms assessment, daily activities that are limited by breathlessness, impact assessment (social functioning, psychological disturbances), and total score. The scores range from 0 to 100 and higher scores indicate more limitations.[25] A mean change score of 4 units is associated with slightly efficacious treatment, 8 units for moderately efficacious change, and 12 units for very efficacious treatment for patients with asthma and COPD.[26]

Depression, Anxiety, Stress Scale-21 is a 3-part instrument used to measure the severity levels of depression, stress, and anxiety. The tool has been accepted and validated for use in PR programs in COPD.[27] Depression scores vary from 0 to 28, anxiety scores vary from 0 to 20, and stress scores vary from 0 to 34, with higher score indicating more severe impairment in the item being evaluated. Scores of 0-9 in the depression item, 0-7 in the anxiety item, and score of 0-14 in the stress item are considered to be normal.

The primary objective was (a) to explore the feasibility of a 6-week PR program in COVID ARDS survivors and the secondary objective was (b) to evaluate the impact of PR on functional capacity, QOL, and mental health indices of COVID-19 ARDS survivors.

The study was carried out at the center for PR in the Department of Pulmonary Medicine of the institute. Approval was sought from Institutional Ethics Committee, and written informed consent was obtained from all participants enrolled in the study. The center for PR is equipped with treadmills and cycle ergometers for aerobic exercises and weights for anaerobic/strength training exercises. The

sessions were supervised by a trained staff as well as a resident doctor. Patients with COVID pneumonia after being discharged from ICU were offered a supervised PR program for 6 weeks consisting of 2 sessions per week. All the patients had a P/F ratio ≤ 200 at least for 1 day during their stay in the ICU. Patients who either did not consent to participate in the program or defaulted within the first 2 weeks (≤4 sessions) were enrolled as controls for comparative assessment. Out of these 13 controls, 4 had defaulted within 2 weeks of enrollment and 9 refused to participate. There were no exercise-induced side effects in defaulters. Most common reason to default or not to participate was related to logistics and transportation to the hospital. After going through baseline evaluation, they were called only after 6 weeks for the final assessment

In the PR program, exercise training included a minimum of 2 supervised training sessions per week to all patients. Exercise sessions consisted of 15-30 minutes of both aerobic and anaerobic exercises including a warm-up and cooldown period. Warm-up included a gentle range of motion exercises for both upper and lower limbs with 10-15 repetitions of each exercise. This was followed by endurance training using a treadmill and stationary cycle. Speed of the treadmill was initially set at 70% of the baseline 6MWT speed with a weekly progression of 0.25 km/h in conjunction with the guidance of modified BORG score. Strength training for quadriceps and upper limbs was given using elastic resistance bands, weight cuffs, and dumbbells. Stretching and breathing exercises including diaphragmatic breathing, pursed-lip breathing, and sustained maximal inspiration with a spirometer were also included in each session.

Baseline parameters assessed at the start of the PR program (0 weeks) consisted of a 6MWD, ISWD, spirometry, mMRC score, SGRQ, BDI, and DASS-21 scores. Baseline assessment also comprised echocardiography to rule out any alternative cause of exercise limitation like major cardiac disease, pulmonary hypertension, or pulmonary embolism. The repeat assessment of these parameters along with calculation of TDI was performed after 6 weeks of supervised PR program. All patients were allowed to recover from their illness to an extent where they were able to maintain oxygen saturation above 90% on room air before being enrolled into PR. The time of enrollment into PR after discharge varied from 1 week to 4 weeks.

Statistical Analysis

We have summarized numerical data using mean and standard deviation and categorical data as account and percentage. For the comparison of numerical parameters across 2 groups, we have used *t*-test or Mann–Whitney *U* test depending upon the distribution of data. Change in scores before and after was calculated and compared between 2 groups. We considered *P* value less than .05 as statistically significant.

RESULTS

A total of 14 patients completed the PR program and 13 patients who either did not give consent or defaulted within 2 weeks of enrollment were taken as controls for this study. Table 1 summarizes the baseline features of both groups. There was a gender difference in PR group with only 1 female and 13 males (*P*-value of .33). Further analysis was not carried out separately for 2 gender groups as only 1 patient in the female group could not be compared with 13 patients in the male group. There was no significant difference in the mean age, mean ICU stays in days, body mass index/fat-free mass index, or proportion of patients on mechanical ventilation/non-invasive ventilation and thus ensuring the homogeneity of the control and PR group.

In our study, significant resolution of the radiologic changes was noted in follow-up computerized tomography (CT) scans of a few patients done in both groups. Figure 1a and b depict pre- and post-intervention CT scans showing significant improvement in a 46-year-old male who underwent PR. Figure 1a shows diffuse ground glass opacities (GGOs) predominantly in lower zones bilaterally, whereas Figure 1b shows complete resolution of these opacities and reveals normal lung parenchyma. Similar improvement is shown in another 36-year-old female who did not opt for enrollment into PR (Figure 1c and d). Figure 1c shows diffusely interspersed GGOs as well as inter and intralobular septal thickening, whereas Figure 1d shows almost complete resolution of these opacities and normal lung parenchyma. The CT findings were almost similar in other patients as well as in both groups. Most of the patients were unable to perform the forced vital capacity (FVC) maneuver as per standards at

Table 1. Baseline Features of Control Group and PR Group

Baseline Feature	Control Group (n = 13)	PR Group (n = 14)	*P*
Gender			
Male, n (%)	7 (53.8)	13 (92.9)	.33
Female, n (%)	6 (46.2)	1 (7.1)	
Mean (SD) age (years)	56.8 (8.7)	57.6 (10.1)	.7
Mean (SD) BMI (kg/m^2)	26.4 (5.2)	25.0 (2.6)	.6
Mean (SD) FFMI	19.4 (2.7)	19.4 (1.7)	.7
Mean duration of ICU stay in days (SD)	10.76	10.64	>.9
Invasive ventilatory requirement, n (%)	3 (23.1)	4 (28.6)	>.9
NIV/HFNC FiO2 requirement, n (%)	10 (76.9)	11(71.4)	>.9

BMI, body mass index; FFMI, fat-free mass index; SD, standard deviation; ICU, intensive care unit.

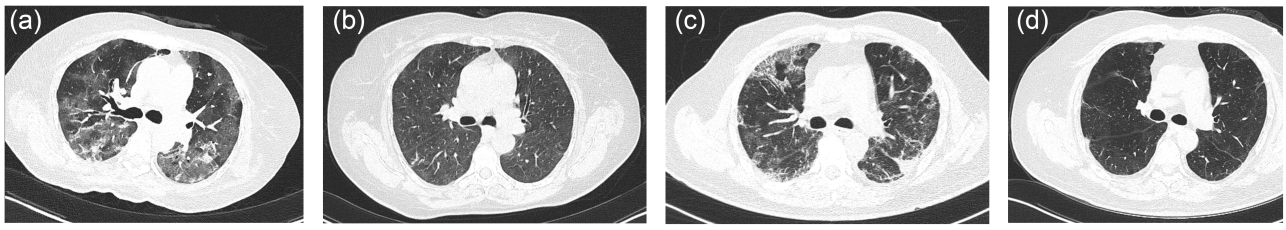


Figure 1. (A) HRCT thorax scan of 46-year-old female after recovery from ICU showing bilateral patchy GGOs predominantly in lower and middle zones (before enrollment into a PR program). (B) HRCT thorax scan of the same patient described in (A) after completion of a 6-week PR program shows marked resolution of the opacities. (C) HRCT thorax scan of 36-year-old male after recovery from ICU showing bilateral patchy GGOs predominantly in lower, middle zones, and subpleural areas. (D) HRCT thorax scan of the same patient described in 2(A) after 6 weeks (without PR intervention) also shows marked resolution of the opacities. ICU, intensive care unit; PR, pulmonary rehabilitation; GGOs, ground glass opacities.

the time of enrollment despite multiple attempts as they had not recovered fully so we could not use pulmonary function tests (PFTs) for comparison on follow-up. Among the patients who were able to perform PFT maneuvers, most of them had moderate restriction on spirometry at the time of enrollment with a mean FEV_1/ FVC of 69.3 ± 10.3% in control and 66.3 ± 24.7% in PR group.

Table 2 shows the details of parameters assessed at 0 and 6 weeks in both the groups.

(a) *Exercise Capacity*: Six-minute walk distance was assessed in all patients at initial assessment (0 weeks) and then at 6 weeks (completion of PR program) as per established ATS guidelines.[17] There was no statistically significant difference in the mean baseline values of 6MWD at 0 week in control and PR groups (320.6 m and 329.3 m, respectively). But, the 6MWD values were statistically and significantly different at 6 weeks in both groups (360.9 m in control group and 496.4 in PR group). Also, the change between 2 groups (40 m and 167.1 m in control and PR group, respectively) was statistically significant with a *P*-value of less than .001, thus highlighting the effect of PR on functional capacity. Also, it needs to be mentioned again that MCID in 6MWD in cardiorespiratory diseases has been reported as 54-80 m, which in our study could be achieved in the PR group.[19] Exercise capacity was also measured via ISWT. There was a mean improvement of 64.9 m in the control group at 0 and 6 weeks, whereas it was 152.5 m in the PR group with the difference between the 2 being statistically significant with a *P*-value of .02 (Figure 2a). To recapitulate, the MCID for ISWD has been reported between 35 and 78 m in previous studies.[20,21] The improvement was more than MCID in both PR group and control group for ISWD.

Table 2. Changes in Various Parameters Measured at 0 and 6 Weeks

	0 Week			6 Weeks					
	Mean (SD)			Mean (SD)			Change		
Parameter	Controls	PR Group	*P*	Controls	PR Group	*P*	Controls	PR Group	*P*
mMRC	2.1 (0.9)	2.5 (0.5)	.2	0.8 (0.6)	0.5 (0.5)	.3	−1.3 (0.8)	−2.0 (0.6)	.010
6MWD	320.6 (100.6)	329.3 (86.9)	.6	360.9 (97.0)	496.4 (67.9)	.002	40.3 (44.0)	167.1 (82.2)	<.001
ISWD	243.6 (107.2)	218.2 (52.9)	>.9	308.5 (82.1)	370.7 (74.7)	.080	102.3 (101.5)	199.3 (139.1)	.025
SGRQ S	27.1 (15.5)	28.3 (16.8)	>.9	20.9 (13.1)	33.1 (15.9)	.061	−6.2 (15.9)	4.9 (16.0)	.085
SGRQ A	54.2 (22.2)	56.8 (20.6)	.7	34.6 (18.6)	47.2 (14.4)	.072	−19.6 (13.7)	−9.6 (26.4)	.076
SGRQ I	31.0 (24.8)	32.1 (18.2)	.5	21.7 (19.4)	17.7 (13.4)	.8	−9.3 (15.0)	−14.5 (17.6)	.6
SGRQ T	37.4 (20.2)	39.0 (15.6)	.5	25.0 (16.5)	29.2 (11.8)	.2	−12.4 (10.2)	−9.8 (17.2)	.4
DASS S	7.4 (5.4)	6.9 (4.8)	>.9	2.3 (2.3)	6.7 (7.6)	.081	−5.1 (4.1)	−0.1 (6.4)	.030
DASS A	7.2 (5.4)	8.8 (5.2)	.5	3.4 (2.2)	7.6 (8.0)	.14	−3.8 (4.3)	−1.2 (6.3)	.4
DASS D	4.3 (4.5)	6.9 (4.8)	.2	1.8 (2.6)	4.4 (4.4)	.055	−2.5 (3.0)	−2.4 (4.8)	.7
BDI total score	5.9 (1.1)	5.9 (1.6)	.8						
TDI total score	–	–	–	6.6 (1.9)	7.1 (1.6)	.6			

6MWD, 6-Minute Walk Test; SGRQ, significant improvement in quality of life; DASS, Depression, Anxiety, Stress Scale; BDI, Baseline Dyspnea Index; TDI, Transitional Dyspnea Index.

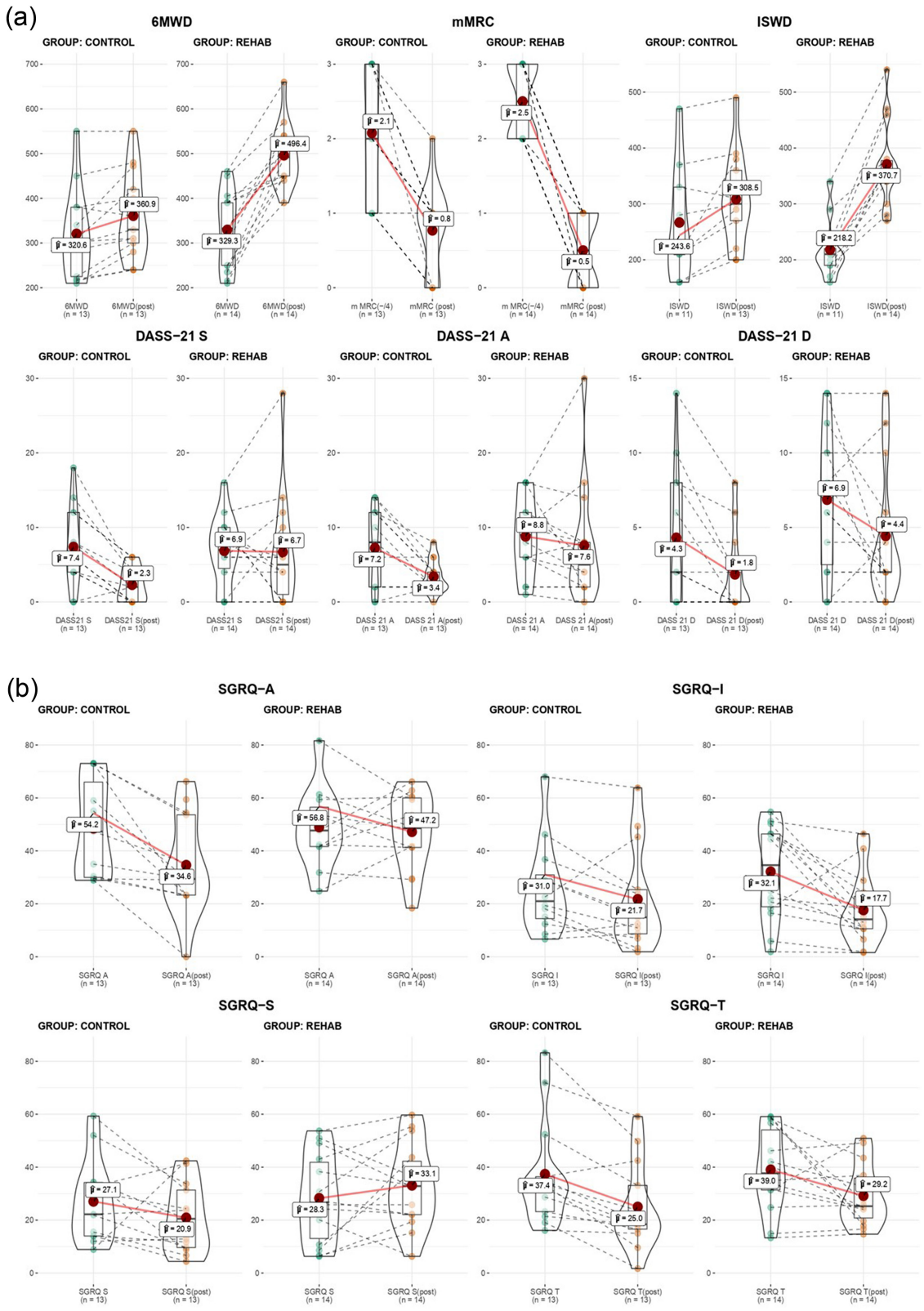


Figure 2. (A) Box violin plot comparing the various parameters namely 6MWD, mMRC, ISWT, DASS-21 stress, DASS-21 anxiety, and DASS-21 depression scores in the control and PR group. The bold line depicts the change in mean values, and the dotted lines reflect the change in individual values in each graph. (B) Box violin plot comparing SGRQ symptom, SGRQ activity, SGRQ impact, and SGRQ total score in the control and PR group. The bold line depicts the change in mean values, and the dotted lines reflect the change in individual values in each graph. 6MWD, 6-Minute Walk Test; DASS, Depression, Anxiety, Stress Scale; ISWT, Incremental Shuttle Walk Test; SGRQ, significant improvement in quality of life.

(b) *Dyspnea Index:* In our study, mean mMRC score improved from 2.1 to 0.8 in the control group and from 2.5 to 0.5 in the PR group. Mean change in the control group was −1.3 and that in the PR group was −2.0 (Figure 2a). Though dyspnea improved in both groups, the decrease in mMRC score was significantly more in the PR group as compared to the control group with a *P* value of .01. We also measured the BDI and TDI as mentioned in the Methodology section. Change in TDI was 6.6 ± 1.9 in the control group and 7.1 ± 1.6 in the PR group suggesting significant improvement in the perception of dyspnea in both groups. *P* value for change in TDI for PR and control group was .6 suggesting that PR did not confer any additional benefit in this domain if this parameter was used for assessment.

(c) *Quality of Life:* In the SGRQ symptom assessment, the mean score decreased from 27.1 to 20.9 in the control group but paradoxically and surprisingly increased from 28.3 to 33.1 in the PR group. In the activity and impact domains of SGRQ, there was an improvement in both the control and PR groups, and the difference in improvement between the 2 groups was statically insignificant. The mean score decreased from 54.2 to 34.6 in the control group and 56.8 to 47.2 in the PR group. In the SGRQ impact domain, the mean score decreased from 31.0 to 21.7 in the control group and 32.1 to 17.7 in the PR group. There was no statistically significant difference in the change in the total SGRQ score as well, the change being 37.4 to 25 in the control group and 39 to 29.2 in the PR group. However, the improvement in each component of SGRQ with respect to the baseline values was noticeable in each group individually (Figure 2b).

(d) *Psychological parameters*: The score in all the 3 items of DASS-21 in our patients was surprisingly normal. The stress score however decreased from 7.4 to 2.3 in the control group and from 6.9 to 6.7 in the PR group. Anxiety score decreased from 7.2 to 3.4 in the control group and from 8.8 to 7.6 in the PR group. Similarly, the change in depression score was from 4.3 to 1.8 in the control group and from 6.9 to 4.4 in the PR group. There was no statistical difference in the change of scores of both depression and anxiety in the 2 groups (Figure 2a). The statistically significant and paradoxical difference in improvement in the stress score of the control group over the PR group is also likely clinically irrelevant, as the 2 groups though having different baseline scores still lied within the normal range of the stress score.

DISCUSSION

The previous literature available about the complications of SARS-related ARDS survivors suggests that these patients do suffer from restrictive lung dysfunction, dyspnea, and impaired QOL as was seen in our study.[9,28] Similar findings have now been reported in COVID ARDS survivors as well, especially from ICUs. These symptoms have been associated with prolonged bed rest, usage of steroids, and varying degrees of muscle weakness. Persisting symptoms for up to 4-12 weeks after the initial onset have been called as "ongoing symptomatic COVID 19" and those lasting beyond 12 weeks have been now labeled as "Long COVID" or "Post-COVID-19 syndrome."[29,30]

Before COVID, PR has been tried in patients of SARS ARDS survivors with promising results. Lau et al[31] carried out a 6-week PR program in 133 patients of SARS after discharge and noted significant improvement in 6MWD, maximal rate of oxygen consumption, and the strength of some specific muscle groups.[31] In another small study from China, PR in post-SARS patients helped them attain better dyspnea scores.[32] Daynes et al[29] very recently not only advocated the feasibility of PR in COVID ARDS survivors based on the 30 patients enrolled in their study but also documented significant improvements above MICDs in exercise capacity and QOL parameters.[29] Similar encouraging outcomes have also been published by Gloeckl et al[30] who implemented PR in 50 COVID patients, 24 with mild/moderate disease and 26 with severe COVID pneumonia.[30]

In a recent data on 3 months follow-up of 125 COVID ARDS patients, although abnormal findings were reported in CT scans of 72% patients, fibrotic changes were present in only 21%.[33]

In our study, significant improvement with PR was seen in indices measuring dyspnea and exercise capacity as evaluated by mMRC score and 6MWD/ISWD, respectively, though these parameters improved in the control group also. Using mMRC scale, dyspnea improved in both control and PR groups (from 2.1 to 0.8 in the control group and from 2.5 to 0.5 in the PR group), the change in latter being statistically more than the change in the former group. The change was also evident when TDI was used as the measuring index; however, this time the change was insignificant in both control and PR groups (6.6 ± 1.9 and 7.1 ± 1.6, respectively).

This compels us to mention about a possible component of natural and spontaneous recovery in such patients, which has also been suggested by other authors.[29] Similarly, improvements were noted in 6MWD and ISWD in both control and PR groups in our study. The improvement although was more in the PR group, the improvement in the control group nearing MCID also cannot be ignored and again emphasizes at least in part the possibility of spontaneous resolution/recovery in these patients. It needs mentioning that we did not use any antifibrotics in the patients enrolled in this study in either of the 2 groups.

Acute respiratory distress syndrome survivors do demonstrate decrements in QOL after discharge. We assessed QOL by SGRQ that performs better with a 3-month or a 12-month recall as compared to a 1-month recall.[26,34] However, we need to highlight that we extended the use of this tool within a month after ICU discharge of the patients. The extent of disability in QOL as assessed by the SGRQ total score improved in both our groups with time and PR could not provide any additional benefit. The small number of patients or the inherent nature of the tool designed to use it for a longer recall period is to be considered before interpreting this section of results. In the SGRQ activity and impact domains, there was a minimal and insignificant improvement in both the control

and PR groups. However, in the symptom domain, the mean score decreased in the control group but paradoxically and surprisingly increased in the PR group.

The reason for this paradoxical observation could be that the SGRQ has been traditionally used for chronic respiratory disease and it was extrapolated for the assessment of QOL in a disease of relatively shorter duration. Also, in the symptom domain of SGRQ, more weightage is given to cough and sputum production as compared to functional capacity. Pulmonary rehabilitation offers little benefit in cough and sputum production.[35] Exercise-induced bronchoconstriction leading to cough in patients of bronchiectasis can be a cause of this paradoxical observation.[36] In a study in patients with bronchiectasis, it was shown that though PR improves dyspnea and fatigue, it does not improve cough-related QOL in patients with bronchiectasis.[13] Nakazawa et al[37] in their review on rehabilitation in interstitial lung disease also mentioned that the efficacy of PR in reducing cough is unclear.[37]

As with any severe illness, COVID ARDS has its effects on mental health as well. Underlying mechanisms proposed include viral infection, immunological response, corticosteroid therapy, and ICU stay.[38] In a study done at Hong Kong in SARS survivors, there was an increase in psychiatric symptoms from 3% to 40% even at 4 years of post-ICU discharge.[39] The psychiatric assessment in our patients revealed only mild disturbances, the reason for which we assume to be the positive effect of surviving a severe disease that has caused significant mortality worldwide overshadowing the mild physical and mental impairment associated with it. Also, the significant improvement in dyspnea and exercise capacity with every passing day in most of our patients would have contributed to a positive outlook of our patients toward their disease and a lesser score on the DASS-21 Scale. The further decrease in DASS-21 scores on follow-up in both the groups further endorses the aforementioned assumption. Less number of female participants and small sample size could also have contributed to this paradoxical observation. Another factor to be mentioned is the applicability of this score itself could be questionable because in existing literature this score has been used in COPD patients only, which is a trademark for chronic respiratory disease.

As we now understand, there is still a lack of clarity in the disease outcome patterns of COVID-19. However, since PR is a very cost-effective strategy and has already proven its importance and worth in various other respiratory diseases worldwide, its implementation needs to be extended to a larger needy population in the country including the COVID-19 ARDS survivors.

Limitations

The first limitation is the small number of patients and controls in the study. But, since there is minimal literature available on this subject, especially from the Indian subcontinent, this is the initial experience from our center, and we expect to present and share a larger data in the next few months. Also, in the PR group, we could not ensure gender homogeneity as only 1 out of 14 patients was female. Second, certain tools like SGRQ and DASS-21 have been traditionally used for chronic respiratory diseases in the past. However, since this study was carried mainly as a feasibility study, the use of these tools was extended to COVID ARDS survivors who had a shorter duration of illness.

CONCLUSION

Pulmonary rehabilitation is feasible in COVID ARDS survivors as 15 out of 19 patients who started the PR successfully completed the program. PR significantly improved the dyspnea and exercise capacity of post-COVID ARDS survivors. But the improvement in the control group was also comparable to MCID mentioned in the literature. However, its benefit in improving perceived dyspnea, QOL, and psychological parameters was not found to be significant in this analysis though these parameters improved with time in both the groups. This signifies the possibility of a relatively fast, self-healing process in these COVID ARDS patients, which brings them to their routine within a few weeks after discharge from the hospital. Thus, the PR program is feasible in this population, and the positive results in the improvement of exercise capacity encourage us to continue recruiting more patients and come out with a larger database in the future.

Ethics Committee Approval: This study was approved by Ethics committee of All India Institute of Medical Sciences Bhopal,India University, (Approval No: IHEC-LOP/2021/ IM0333).

Informed Consent: Verbal and Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.K.K., A.H.; Design – A.K.K., A.H., A.G.; Supervision – A.K.K., M.V., A.G., A.H., B.S.; Resources – A.K.K., A.H., S.T.K., S.S., M.V., G.S., .B.S.; Materials – A.K.K., B.S., A.H., S.K.; Data Collection and/or Processing – A.K.K., S.G., A.G., .S.K., G.S.; Analysis and/or Interpretation – A.K.K., .A.H.; Literature Search – A.H., A.K.K., G.S., S.K.; Writing Manuscript – A.K.K., A.H., S.K., S.S.; Critical Review – A.K.K., A.G., A.H., R.S., S.K., S.T.K.

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Original Article

Altered Cardiac Repolarization in Chronic Obstructive Pulmonary Disease

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Abstract

OBJECTIVE: Altered cardiac repolarization is an important mechanism in the development of malignant cardiac arrhythmia and in the occurrence of sudden cardiac death. It is known that the risk of cardiac arrhythmia and sudden death is increased in patients with chronic obstructive pulmonary disease. Evaluating the measurements of repolarization in the electrocardiogram may provide useful information to determine potential risks for lethal arrhythmias in the patients with chronic obstructive pulmonary disease. In the present study, we investigated the possible relationships between repolarization parameters in the electrocardio and demographic, clinical, and biochemical findings in patients with chronic obstructive pulmonary disease.

MATERIAL AND METHODS: In the present study, 35 patients with Global Initiative for Chronic Obstructive Lung Disease A-B constituted group 1 and 35 patients with Global Initiative for Chronic Obstructive Lung Disease C-D constituted group 2. Cardiac repolarization and dispersion (QTc interval and QT dispersion) were measured on 12-lead electrocardiogram. QTc interval, QT dispersion, TP-e, and Tp-e/QTc were evaluated in order to determine the patients at risk of sudden cardiac death. QTc interval >440 ms in men and >460 ms in women was considered as prolonged QTc interval.

RESULTS: QTc and QTd values were found to be statistically significantly prolonged in the group of GOLD C-D compared to the group of GOLD A-B ($P < .001$). QTc value showed negative correlation with the ratio of forced expiratory volume in 1 second to forced vital capacity and partial pressure of oxygen ($P = .030$, $r = -0.260$; $P = .006$, $r = -0.332$, respectively). No significant difference was in Tp-e and Tp-e/QTc between the groups ($P = .73$, $P = .12$, respectively).

CONCLUSION: QTc and QTd are non-invasive markers reflecting arrhythmogenicity, and our findings were found to be related to prolonged QTc and QTd in patients with chronic obstructive pulmonary disease. Prolongation in the dispersion of repolarization and altered cardiac repolarization in the population with chronic obstructive pulmonary disease may be related to hypoxemia and airway obstruction. Alterations in the cardiac repolarization may put these patients at high risk for malignant ventricular arrhythmia and sudden cardiac death.

KEYWORDS: Cardiac repolarization, chronic obstructive pulmonary disease, QT interval
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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of mortality in the world and is estimated to gain a third place by 2020. In 2012, COPD, which caused 6% of all deaths worldwide, killed over 3 million people. Chronic obstructive pulmonary disease is both a preventable and treatable disease which represents a serious public health issue. Chronic obstructive pulmonary disease is one of the main causes of chronic morbidity and mortality worldwide and considerably increases mortality rates due to its complications.[1] Most COPD patients are likely to have a previously existing cardiovascular disease and are at great risk of acute incidents, hospitalizations, and cardiovascular-related morbidity.[2,3]

Due to this strong association, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) considers cardiovascular diseases concomitant with COPD as the most significant disease and strongly recommends that COPD patients be routinely screened for cardiovascular diseases; however, they do not provide any recommendations as to how this should be done.[4]

It is known that COPD patients are at increased risk of cardiac arrhythmia and sudden death.[5-7] Remodeling of cardiac repolarization is an important mechanism in terms of the occurrence of malignant arrhythmia and sudden cardiac death.[8-10] The QT interval (QT) and QT dispersion (QTd) are electrocardiogram (ECG) parameters used to evaluate myocardial repolarization.[11] The heterogeneity and dynamics of QT interval are used to indicate increased sensitivity in ventricular arrhythmias.[12] Circadian changes may be observed in the normal heart depending on the QT interval, autonomic circulation, and increased catecholamine concentration changes.[13] The QT interval reflects homogeneity of ventricular

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repolarization. Prolonged QT interval is an indicator of cardiac repolarization abnormalities.[14]

In order to determine the potential risks of life-threatening arrhythmias, evaluation of ECG repolarization measurements will provide clinically beneficial information in this patient population. In this study, we investigated the demographic, clinical, and biochemical data of ECG repolarization indicators in COPD patients.

MATERIAL AND METHODS

The study population consisted of patients with COPD diagnosis according to the GOLD criteria and confirmed with post-bronchodilator ratio of forced expiratory volume in 1 second to forced vital capacity (FEV1/FVC) <70 criteria, who presented to the University Hospital between January 2018 and June 2018. Forced expiratory volume in 1 second (FEV1) percentage according to the expected value was used for determining the grade (1-4) of obstruction severity of COPD, as also suggested by the 2017 GOLD report. The most important revision of this report was the removal of the FEV1 value from the combined assessment. Therefore, unlike the 2011 GOLD report, A-D categories were only defined according to exacerbation risk and symptom severity. This revision completely excluded FEV1 from pharmacological treatment decision-making. On the other hand, the report emphasizes that FEV1 still remains an important factor in determining the severity and prognosis of the disease, as well as non-pharmacological treatment decision-making. In order to assess symptoms, the GOLD reports recommend the use of the COPD Assessment Test or Modified Medical Research Council Dyspnea Scale (mMRC).

Accordingly, cases followed up with COPD diagnosis for the last 5 years were classified using the GOLD criteria. The 35 cases who were GOLD A-B formed group 1 and the 35 GOLD C-D cases comprised group 2. Patients with ischemic heart disease, heart failure, acute myocardial infarction, heart valve disease, branch block in ECG, atrial fibrillation, drug use causing QT dispersion (such as probucol, terfenadine, amiodarone, erythromycin, clarithromycin), and electrolyte disorder were excluded from the study.

MAIN POINTS

- The underlying mechanisms of the relationship between chronic obstructive pulmonary disease (COPD) and sudden cardiac death are still largely unknown, and the markers of malignant cardiac arrhythmia and sudden cardiac death in COPD have not been identified.
- Prolonged QT interval and increased QT dispersion are indicators of increased risk of malignant cardiac arrhythmia and sudden cardiac death.
- Cardiac repolarization remodeling and increased repolarization dispersion may be associated with increased hypoxemia and airflow obstruction in COPD patients.
- Therefore, we believe that increased cardiovascular risk should be kept in mind when managing highly symptomatic COPD patients who undergo more frequent exacerbations.

Pulmonary function tests were performed by the same nurse on patients, who were previously informed on how it would be conducted, sitting 90 degrees upright, using a ZAN 300 spirometer. Spirometry tests were repeated at least 3 times, in which the one with the best results was used for evaluation. All study participants underwent a 12-derivation ECG, which was recorded at 50 mm/s paper speed. Electrocardiogram recording was delayed in patients with the blood pressure of 160/100 mmHg and higher. Precordial V2-V6, which best shows the QRS complex, was used for ECG measurements. Measurements were made by 2 different cardiologists, and in the case when different measurements were yielded, the average of the 2 measurements was used. The QT interval was measured as m/s units from the start of the Q wave to the point at which the T wave returned to the isoelectric line. In ECGs with U wave, the lowest point between the T and U waves was considered the end of the T wave. Derivations in which the T wave's end could not be determined were not analyzed. QT interval correction for heart rate was calculated using Bazzett's formula ($QT/\sqrt{R-R}$).

The mean of 3 consecutive corrected QT interval (QTc) in each derivation was considered the QTc interval for that derivation. Patients with QTc interval for at least 9 derivations were included in the study. Tp-e was measured as the distance between the projection of the peak of the T wave on the isoelectric line and the projection of the line connecting the descending limb of the T wave on the isoelectric line. Together with these measurements, the Tp-e/QTc ratios were also calculated. All measurements were taken manually. The correlations between clinical and laboratory results of the patients and ECG repolarization parameters were analyzed. The study was approved by the University Ethics Committee with protocol number 47 and informed written consent was obtained from all participants.

Statistical Analysis

Conformation of normal distribution of the data was tested using the Kolmogorov–Smirnov test. Data with normal distribution were compared with independent paired samples *t*-test. Group comparisons of variables without normal distribution were assessed using the Mann–Whitney *U* test. Distribution correlations of categorical variables were analyzed using the chi-squared test and Fischer's exact test. Logistic regression analysis was used to estimate QTc groups. The relationship between quantitative variables was examined with the Spearman correlation test. Statistical parameters were expressed as mean, standard deviation, median, q1 (25% quartile), and q3 (75% quartile) values. Statistical significance was accepted as $P < .05$. Data were analyzed using the International Business Machines Corporation Statistical Package for the Statistical Package for Social Sciences 22.0 (IBM SPSS Corp.; Armonk, NY, USA) package program.

RESULTS

Group 1 consisted of 35 patients who met GOLD A-B criteria, while group 2 included 35 patients who met GOLD C-D criteria. The demographic and clinical features of the groups are presented in Table 1. There was no significant difference between the groups according to age, gender, BMI, history of smoking, and mMRC score ($P = .10$, $P = .160$, $P = .92$, $P =$

.63, $P = .07$, respectively). FEV1, forced vital capacity (FVC), and FEV1/FVC levels were significantly higher in group 1 compared to group 2 ($P < .001$). The mean number of exacerbations/hospitalizations was significantly higher in group 2 compared to group 1 ($P < .001$) (Table 1).

QTc value was significantly higher in group 2 compared to group 1 ($P < .001$). Comparison of QTc values among the groups showed that 30 cases in group 1 (71.4%) were QTc negative and 5 were QTc positive (17.9%). In group 2, 12 cases were QTc negative (28.6%) and 23 were QTc positive (82.1%). Comparison of QTc positivity and negativity among the groups was statistically significant ($P < .001$) (Table 2, Figure 1). QTc value showed negative correlation with FEV1 and P_aO_2 ($P = .032$, $r = -0.257$; $P = .006$, $r = -0.332$, (Figures 2, 3) respectively). In the regression analysis of QTc and other variables, it was found that there was no correlation with age, smoking, BMI, and mMRC score ($P > .05$) and only correlated with the number of hospitalizations and exacerbations ($P < .001$) (Table 3). QTd value was significantly higher in group 2 compared to group 1 ($P < .001$). There was no difference between the groups according to Tp-e and Tp-e/QTc ($P = .73$; $P = .129$) (Table 1).

DISCUSSION

In this study, we reached 2 important conclusions. The first was that QTc and QTd were significantly higher in GOLD C-D patients compared to GOLD A-B patients. The second

Table 1. Demographic and Clinical Features of the Groups

	Group 1 GOLD A-B	Group 2 GOLD C-D	*P*
Age (years)	62.37 ± 8.82	66.00 ± 9.36	.100
Gender (n %)			
Male	31 (88.57%)	34 (97.14%)	.164
Female	4 (11.43%)	1 (2.86%)	
BMI (kg/m^2)	25.64 ± 3.97	25.54 ± 4.98	.928
Smoking (packs/year)	40.60 ± 21.69	43.03 ± 21.20	.637
mMRC (n %)			
0	6 (17.1%)	2 (5.7%)	.070
1	16 (45.7%)	11 (31.4%)	
2	5 (14.3%)	3 (8.6%)	
3	8 (22.9%)	17 (48.6%)	
4	0 (0%)	2 (5.7%)	
Exacerbation/hospitalizations (n %)			
<2	35 (100%)	0 (0%)	**.001***
>2	0 (0%)	35 (100%)	
ECG parameters			
QTc	412 (400-434)	461 (418-462)	**<.001***
QTd	40 (20-40)	60 (20-80)	**.013***
Tp-e	90 (80-100)	80 (60-110)	.734
Tp-e/QTc	0.22 (0.19-0.24)	0.19 (0.15-0.26)	.129
Pulmonary function tests			
FVC (L)	3.43 (2.29-3.88)	2.42 (2.02-3.29)	**.032***
FVC % predicted	0.90 (0.72-1.00)	0.66 (0.55-0.89)	**.007***
FEV1 (L)	2.08 (1.08-2.43)	1.26 (0.89-1.92)	**.020***
FEV1 % predicted	0.65 ± 0.22	0.50 ± 0.22	**.008***
FEV1/FVC	0.62 (0.54-0.64)	0.54 (0.46-0.62)	**.038***
Laboratory results			
pH	7.42 (7.40-7.43)	7.41 (7.38-7.44)	**.307**
PCO_2 (mmHg)	32.90 ± 4.68	37.17 ± 6.41	**.002***
PO_2 (mmHg)	87.17 ± 16.60	63.26 ± 18.89	**<.001***
SAO_2	97.00 (95.50-97.60)	92.00 (85.80-94.40)	**<.001***

GOLD, Global Initiative for Chronic Obstructive Lung Disease; BMI, body mass index; mMRC, Modified British Medical Research Council; QTc, corrected QT interval; QTd, QT dispersion; Tp-e, the peak and the end of the T wave; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen; SAO_2, oxygen saturation.

Table 2. QTc Positivity-Negativity of the Groups

	QTc					
	Negative		Positive		Total	
	N	%	N	%	N	%
GOLD						
A+B	30	71.4	5	17.9	19.286	***P* < .001***
C+D	12	28.6	23	82.1		

GOLD, Global Initiative for Chronic Obstructive Lung Disease; QTc, corrected QT interval.

was that the remodeling of cardiac repolarization in GOLD C-D patients may be related to the degree of airflow restriction. Remodeling of cardiac repolarization may pose risk for malignant ventricular arrhythmia and sudden cardiac death in these patients.

Chronic obstructive pulmonary disease is associated with increased cardiovascular morbidity and mortality.[2] Previous population-based studies have demonstrated that COPD patients are at 2 to 3 times increased risk of sudden cardiac death.[15] However, the underlying mechanisms of the association between COPD and sudden cardiac death are still unclear, and the reasons behind malignant cardiac arrhythmia and sudden cardiac death in COPD have not been identified. Several factors such as hypoxemia, hypercapnia, acid-base disorders, autonomic dysfunction, and drugs may contribute to arrhythmia development in these patients.

Remodeling of cardiac repolarization is an important mechanism in the development of malignant arrhythmia and sudden cardiac death.[8-10] Measurements obtained from ECG indicate repolarization dispersion and electrical heterogeneity of ventricles during repolarization.[10] Studies have shown an association between measurements showing remodeling of cardiac repolarization, such as in QT interval or [16], QT dispersion, and occurrence of malignant arrhythmia and sudden cardiac death in the cases with cardiac failure,[17] prolonged QT syndrome,[18] and elderly age.[19] Prolonged QT interval and

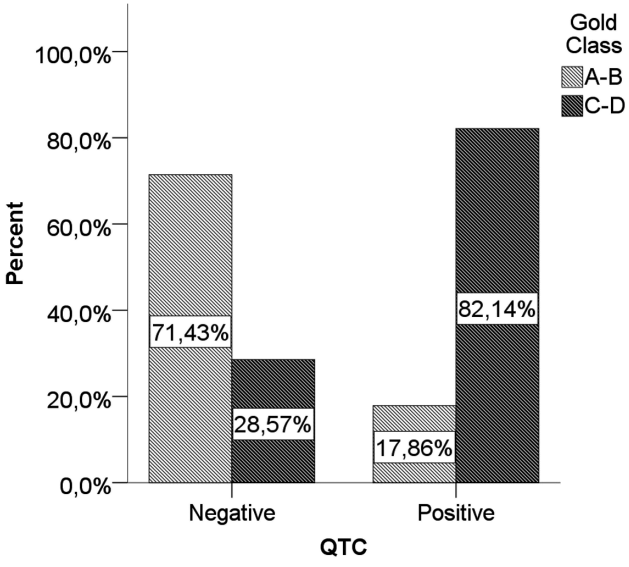


Figure 1. QTc positivity-negativity of the groups.

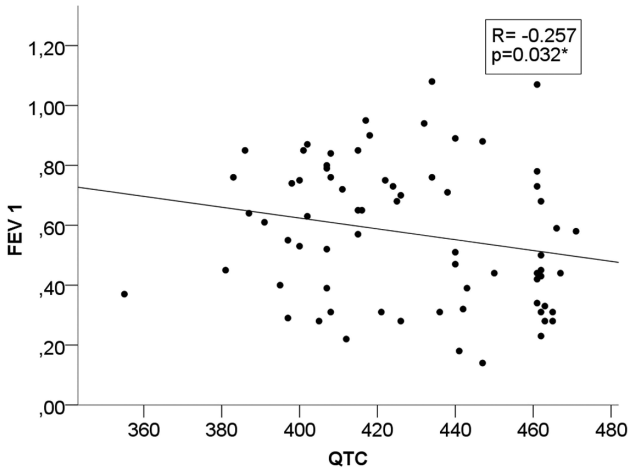


Figure 2. Correlation curve of QTc and FEV_1.

increased QT dispersion are indicators of risk for malignant cardiac arrhythmia and sudden cardiac death.[17,20]

In the sensitivity period of reentrant tachycardia, the QT interval is correlated with ventricular depolarization and repolarization in ECG. Therefore, prolonged QTc of up to >4500 ms has been identified as a risk factor for malignant ventricular arrhythmia and sudden cardiac death.[20,21] QT dispersion reflects spatial differences in myocardial healing time. Previous studies have shown that >60 ms increase in QT dispersion is associated with malignant ventricular arrhythmia[22] and sudden cardiac death.[14] In COPD patients, QT dispersion has been found to correlate with a number of ventricular extrasystoles[23] and a relationship between prolonged QTc interval and sudden cardiac death has been suggested.[24]

Present COPD data is varied due to differences in methodology, diagnostic measures, and analytic approach. Studies have shown that the prevalence of the disease increased in smokers and the elderly, males in developing countries, and equally in both genders or in women in developed countries.[25] In our study, 94.2% of the cases were men and 5.8% were women, while mean age was 64.91 ± 8.74 years in men and 54.80 ± 11.08 years in women. Chronic obstructive pulmonary disease is associated with the risk of cardiac

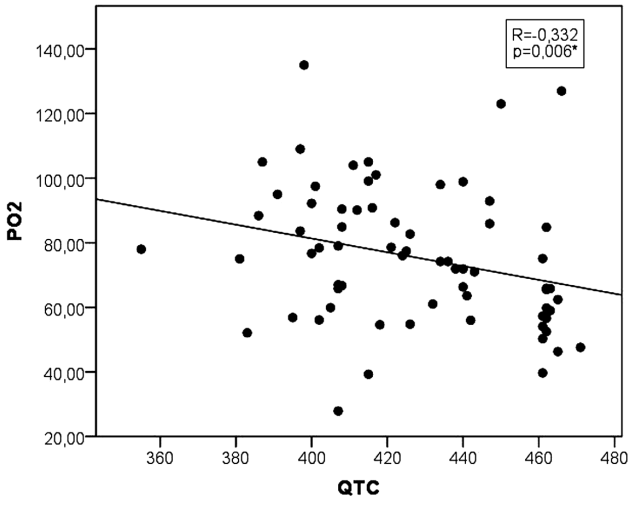


Figure 3. Correlation curve of QTc and P_aO_2.

Table 3. Regression Analysis of QTc

					95% CI OR	
Predictor	**B**	**Wald**	***P***	**OR**	**Lower**	**Upper**
Age	0.011	0.099	.753	1.011	0.946	1.080
Smoking	0.020	1.604	.205	1.020	0.989	1.052
BMI	0.107	2.219	.136	1.113	0.967	1.282
Hospitalizations	−2.282	12.544	**<.001***	0.102	0.029	0.361
mMRC	0.238	0.628	.428	1.268	0.705	2.282

QTc, corrected QT interval; BMI, body mass index; mMRC, Modifiye British Medical Research Council.

arrhythmia. Smoking most likely plays a role in the etiology of both COPD and ischemic cardiac disease. In our study, the smoking history of men and women was mean 40 packs/year.

Some studies have investigated factors which may lead to remodeling changes in cardiac repolarization in COPD patients; however, these studies did not include comorbidities accompanying COPD.[5,22] It is known that about 50% of COPD patients over 50 years of age have coronary artery disease, hypertension, or heart failure which may increase susceptibility to ventricular arrhythmias.[26] In our study, COPD patients without structural heart disease or a history of using cardiac medication were included. These criteria, which limited the number of patients who could be included in the study, were necessary in order to limit the effects of hypoxemia and hypercapnia.

Some evidence points that hypoxemia may prolong repolarization time. Roche et al[27] reported that when healthy subjects were exposed to normobaric hypoxemic conditions, hypoxemia significantly increased QTc interval. Tirlapur et al[7] observed electrocardiographic changes such as prolonged QTc interval in 12 COPD patients with low mean basal SpO_2 (<80%). Sarubbi et al[5] investigated the effects of hypoxemia on QTc dispersion in COPD patients. In the COPD group with hypoxemia, 24-hour oxygen therapy was given, and it was observed that hypoxemia partially resolved and QT dispersion significantly decreased. Their study showed the beneficial effects of correction of hypoxemia and oxygen therapy on lowering increased QT dispersion. It was proposed that hypoxemia affected left ventricular performance, either directly or through sympathetic activity, and that patients with hypoxemic respiratory failure were at increased risk of tachyarrhythmia. Our study investigated how changes in partial oxygen pressure affected QTc value, and it was found that decreased PaO_2 caused an increase in QTc. These findings indicated that changes in blood gas levels may cause increased QTd in COPD patients. Contrary to these studies, Smith et al[28] conducted research on 20 COPD patients and compared groups with desaturation (<90%) and normal saturation, and ischemic ECG changes were not observed in any patient during exercise. No changes in QTc dispersion were observed before or after exercise either. Furthermore, receiving oxygen therapy before and after the test had not affected the QTc value. The aforementioned study did not find any evidence that exercise increased or exacerbated hypoxemia-induced QTc dispersion.[28]

Evidence from long-term studies indicates that decreased FEV1 is associated with an increased risk of ischemic heart failure, cerebral disease, and sudden cardiac death, even after conventional cardiovascular risk factors were eliminated.[29,30] High prevalence of cardiac arrhythmia and severity of airflow obstruction are thought to be associated with the occurrence of arrhythmia in COPD patients.[31,32] In our study, FEV1, FVC, and FEV1/FVC values were significantly lower in the GOLD C-D group compared to the GOLD A-B group, and there was a statistically significant negative correlation between FEV1 and QTc. As the restricted airflow of the cases increased, an increase in QTc values was observed. Contrary to our findings, Tug et al[33] assessed 35 COPD patients who were classified as mild or moderate-severe COPD and found that there was no difference between mild and moderate-severe cases in terms of QT interval or QTc. In a study by Zulli et al.[34] a single-variable analysis of 246 COPD patients without comorbidity showed that FEV1 and FVC were associated with QT dispersion; however, multivariate analysis did not yield a significant correlation. Yildiz et al[22] conducted a small-scale case–control study on COPD patients, in which ventricular arrhythmia was significantly correlated with increased QT dispersion but not with pulmonary function tests, hypoxemia, or degree of hypercapnia. In addition, there was a correlation between the parasympathetic component of heart rate variability and QT dispersion, and it was suggested that autonomic dysfunction may play a role in the development of arrhythmia in these patients.[22]

There is also evidence that autonomic neuropathy may lead to prolonged cardiac repolarization in COPD. Stewart et al[24] compared 17 COPD patients with autonomic neuropathy to 17 COPD patients without autonomic neuropathy and found that QTc measures were significantly longer in those with autonomic neuropathy. They concluded that autonomic neuropathy may also extend QTc.[24] However, our study did not assess autonomic neuropathy, and therefore, our results cannot be directly compared with the results of the aforementioned study.

Our study had some limitations. Standard 12-derivation ECG was used and 24-hour continuous ECG was not conducted. Therefore, it was impossible to evaluate the causal relationship between remodeling of cardiac repolarization, malignant ventricular arrhythmia, and sudden cardiac death. It is currently unknown whether or not prolonged cardiac repolarization induced sudden cardiac death in patients with

COPD. In order to understand whether or not prolonged cardiac repolarization causes malignant ventricular arrhythmia or sudden cardiac death, further controlled longitudinal studies are warranted.

In conclusion, QTc and QTd are noninvasive indicators of arrhythmogenicity, and our findings demonstrate that QTc and QTd are associated factors in COPD. Increased dispersion of repolarization and remodeling of cardiac repolarization in the COPD population may be related to hypoxemia and airflow obstruction. Remodeling of cardiac repolarization may expose an increased risk of malignant ventricular arrhythmia and cardiac death.

CONCLUSION

Chronic obstructive pulmonary disease is a widespread crippling disease and the fourth leading cause of death after ischemic heart disease. Comorbidities are prevalent in COPD and are significant in that they have negative effects on the person's health condition. Increased risk of cardiac arrhythmia and sudden cardiac death are known to be associated with COPD. Cardiac repolarization remodeling may put these patients at high risk for malignant ventricular arrhythmia and sudden cardiac death. Therefore, ECG indicators of repolarization may be important in identifying COPD patients at high risk of developing cardiac arrhythmia.

Ethics Committee Approval: The study was approved by the ethics committee of Sutcu Imam University Faculty of Medicine (Feb 14, 2018; (Approval No:05).

Informed Consent: Written informed consent was obtained from each participant who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Design - F.B.; Resources -F.B., F.A.U.; Materials - F.A.U, F.B., E.A.; Data Collection and/or Processing - F.A.U., F.B.; E.A., N.A., H.K., Analysis and/or Interpretation - F.B., F.A.U., A.D.,; Literature Review - F.B., F.A.U.; Writing – F.B., F.A.U.; Critical Review - F.B.

Declaration of Interests: The authors have no conflict of interest to declare.

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Original Article

Obstructive Sleep Apnea Effects on Pulmonary and Respiratory Muscle Function of Obese Children and Adolescents: A Preliminary Study

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Abstract

OBJECTIVE: Obstructive sleep apnea causes a marked decrease in lung volume and increases lung elasticity in obese adults. However, pulmonary and respiratory muscle function of obese children with obstructive sleep apnea who are more prone to develop airway obstruction than adults is less understood. This study aimed to determine the effects of obstructive sleep apnea on pulmonary and respiratory muscle function in obese children and adolescents compared to those without obstructive sleep apnea.

MATERIAL AND METHODS: This cross-sectional study enrolled 12 obese children and adolescents with a known polysomnographic diagnosis of obstructive sleep apnea and 12 controls that were matched for age, gender, and body mass index. Pulmonary function, maximal inspiratory pressure, maximum voluntary ventilation, and anthropometric variables were measured.

RESULTS Obese children and adolescents with obstructive sleep apnea exhibited significantly lower maximal mid-expiratory flow and displayed a forced expiratory flow at 50% and 75% of vital capacity (all $P < .05$) compared to the control group. However, there were no changes in other pulmonary function variables (all $P > .05$). Their maximal inspiratory pressure and maximum voluntary ventilation were lower than those of the controls, but this was not statistically significant (all $P > .05$).

CONCLUSION: Obstructive sleep apnea did not change pulmonary and respiratory muscle function in obese children and adolescents. The special assessment should be warranted to identify a reduction in maximal mid-expiratory flow and forced expiratory flow at 50% and 75% of vital capacity observed in this population.

KEYWORDS: Children, obesity, pulmonary function, respiratory muscle, sleep apnea
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INTRODUCTION

Obstructive sleep apnea (OSA), the most severe form of sleep-disordered breathing, is commonly found with a prevalence varying from 19% to 61% in obese children.[1] Obstructive sleep apnea in childhood is characterized by repetitive obstruction of the upper airway associated with hypoxia and arousals during sleep and/or increased respiratory effort secondary due to increased upper airway resistance and pharyngeal collapsibility, which subsequently induce sleep fragmentation, systemic alterations, and physical inactivity.[1,2] Studies showed that obstructed airways and hypoxia caused by OSA may overload pulmonary and respiratory muscle function.[3,4] A previous study reported that impaired inspiratory muscles were observed in adults with OSA.[5] Moreover, OSA could be worsened by obesity via mechanical stress upon the respiratory system affecting the diaphragm, lung volume, respiratory muscle function, work of breathing, and ventilator control.[6] A meta-analysis study[7] concluded that obesity causes deleterious effects on some pulmonary function variables including a decline in the ratio of forced expiratory volume in 1 second and forced vital capacity (FEV1/FVC), maximum mid-expiratory flow (MMEF), total lung capacity (TLC), and functional residual capacity (FRC) in children and adolescents. Reduction expressed as FEV1/FVC and the average FEF during the mid-portion of FVC at 50% and 75% of vital capacity (FEF_{25-75}) were more pronounced in children than adults. Additionally, it has been shown that obese adults with OSA, who have decreased lung volume, had a marked increase in the resistance of total respiratory and peripheral airways compared to those without OSA.[8] These results indicate that OSA combined with obesity might cause abnormally increased lung elasticity recoil pressure on exhalation which resulted in an increase in the severity of the airway obstruction. Furthermore, a diminished lung function which correlated with the severity of OSA was observed in obese children and adolescents.[3]

Thus, the aforementioned findings suggest that the coexistence of OSA and obesity may have more deleterious effects on respiratory function. However, it is unclear to what extent OSA combined with obesity has an impact on pulmonary and respiratory muscle function in children and adolescents who had more susceptible to airway obstruction than adults.[9] The understanding of how OSA combined with obesity affects the respiratory system in youth is important to clarify the nature of such disorders and to support clinical decision-making. Thus, the purpose of this study was to investigate the impacts of OSA on pulmonary and respiratory muscle function in obese children and adolescents compared to those without

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OSA. This study's hypothesis stated that obese children with OSA are more likely to be associated with impairments of pulmonary and respiratory muscle function than the controls without OSA.''

MATERIAL AND METHODS

Study Population and Sample Size Calculation

Based on the recommendation from Julious,[10] a flat rule of thumb was used and 12 participants per group would be needed for the pilot study. However, the stepped rule of thumb which requires 10 participants per group for estimating the variance to be used for the main trial sample size calculation provided a power of 90%, type I error rate of 5%, and a large (0.8) effect size.[11] Therefore, 12 obese children and adolescents aged 8-17 years underlying the polysomnographic (PSG) diagnosis of OSA and Sleep-Related Breathing Disorder-Pediatric Sleep Questionnaire (SRBD-PSQ) scores ≥0.33 were voluntarily enrolled. They were recruited at the Snoring Clinic at Chiang Mai University Hospital, Chiang Mai Province. The control group consisted of 12 obese children and adolescents from schools in Muang, Chiang Mai Province, who had SRBD-PSQ scores <0.33 that indicated non-OSA. Both groups were matched by age, sex, and body mass index (BMI). These participants were excluded in case of chest wall abnormalities, asthma, severe medical or mental illness, could not complete the pulmonary function test, or even those who had received any medical treatment that might affect the outcome variables.

Study Design

A cross-sectional study was conducted from February 2019 to January 2020. The protocol in this study was approved by the Ethics Committee of the Faculty of Associated Medical Sciences, Chiang Mai University (AMSEC-62ex-004), and written informed consent was obtained from the participants and their parents before data collection. Primary outcomes were pulmonary function testing, including FVC, FVC% predicted, FEV1, FEV1/FVC ratio, MMEF, $FEF_{25\%}$, $FEF_{50\%}$, and $FEF_{75\%}$, peak expiratory flow (PEF), maximal inspiratory pressure (PImax), and maximal ventilation voluntary (MVV). Secondary outcomes included anthropometric (body weight, stature, BMI, and skinfold thickness) variables. All outcomes were measured by well-trained assessors.

Diagnosis of OSA

Overnight polysomnograms were conducted in the hospital for monitoring PSG indices including the apnea–hypopnea index (AHI), ODI, and oxygen saturation (SaO_2) nadir by using a mobile sleep machine (SOMNOlab 2, Hamburg, Germany).[12] According to the criteria of Katz and Marcus,[13] OSA was defined if a participant had any of the following PSG index values: AHI ≥ 1 time/h or SaO_2nadir < 92%. The severity of OSA was classified based on either the AHI or SaO_2nadir (AHI < 1 or SaO_2nadir ≥ 92 = normal; 1 ≤ AHI < 5 or SaO_2nadir 86-91 = mild; 5 ≤ AHI < 10 or SaO_2nadir 76-85 = moderate; AHI ≥ 10 or SaO_2nadir ≤ 75 = severe).

SRBD-PSQ

The Thai version of 22-item SRBD subscale of PSQ was performed to assess the risk of OSA. The participant was considered to be at risk for OSA if PSQ scores ≥ 0.33.[14]

Experimental Protocol

All participants were seated and performed the anthropometric measurements, PImax, PFTs, and MVV, respectively, with a 5-minute intermission between the tests in the laboratory at a temperature of 25°C and a relative humidity of 56 ± 5%. All tests were completed at the same time of day, and verbal encouragement was provided during testing.

OUTCOME MEASUREMENTS

Anthropometric Variables

Body weight, stature, BMI, and skinfold thickness were determined using standardized techniques. Obesity was defined based on the International Obesity Task Force criteria.[15] Triceps and subscapular skinfold-thickness measurements were measured at the left side of the body using a Lange skinfold caliper (Beta Technology, Calif, USA) according to the standard method.[16]

Pulmonary Function Variables

Pulmonary function testing was conducted by using a computerized spirometer (Chestgraph HI-105; Chest MI Inc., Tokyo, Japan), according to the standardized procedure.[17] Each participant was instructed to sit and perform 2 to 3 trials for vital capacity practice followed by at least 3 acceptable FVC maneuvers. Pulmonary function testing includes FVC, FVC% predicted, FEV1, FEV1/FVC ratio, MMEF or $FEF_{25-75\%}$, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, and PEF were recorded. All values derived from spirometry are expressed as percentages of the predicted values for age and sex.

Maximum Inspiratory Pressure (PImax)

Maximum inspiratory pressure indicator of muscle strength was determined from residual volume (RV) and TLC with MicroRPM® (MICRO Medical®, Rochester Kent, UK) using standard procedures.[18] Participants were asked to perform a maximal inspiratory effort and hold it for 1 second. Three trials with a 1-minute interval between each were taken, and the highest value was chosen.

Maximal Ventilation Voluntary (MVV)

Maximal ventilation voluntary, which indicates the ventilatory mechanics and inspiratory muscle endurance,[19] was conducted according to the ATS/ERS guidelines[18] by using the Chestgraph HI-105 spirometer. Two trials of MVV maneuvers with a 5-minute interval was performed according to a previous study's guidelines.[20] Participants attached a nose clip and were instructed to breathe regularly in and out for 15 seconds with maximal voluntary effort.

Intra-rater Reliability of Data Collection

Each outcome measurements included anthropometry, PFTs and MVV, and PImax and was allocated to 3 raters, whereby the intra-rater reliability was performed. Five participants were chosen to administer each outcome for 2 trials with a 1-day interval between them. The intra-rater reliability of all variables was within an acceptable range (intraclass correlation coefficients (ICCs) > 0.9, all $P < .01$).

STATISTICAL ANALYSIS

The Shapiro–Wilk test was used to test for normality of data. It was found that all outcome variables were normally

distributed. Therefore, the mean and standard deviation (SD) were represented for continuous data. Count and percentage were represented for categorical data. Mean differences in PFTs, PImax, and MVV between the 2 groups were compared using an independent *t*-test. The ICC was calculated to assess the intra-rater reliability of the data collection. Significance was taken as $P < .05$ for all tests. All analyses were performed using the The Statistical Package for Social Sciences version 22.0 software (IBM Corp.; Armonk, NY, USA). Effect size was calculated from the pilot study results using G*Power software application (G*Power version 3.1.9.7 for Windows, Dsseldorf, Germany).

RESULTS

Study Participants

The characteristics of the study groups are given in Table 1. Fifty percent of children and adolescents with OSA had AHI ≥ 1 and all of them had SaO_2nadir < 92%. Based on the SaO_2nadir, the obese with OSA participants had 3 mild OSA (25%), 8 moderate OSA (66.7%), and 1 had severe PSG (8.3%). They were comparable to the obese without OSA group in age, gender, anthropometric variables but were significantly higher in SRBD scores ($P < .05$).

Pulmonary Function Variables

As shown in Table 2, the values of MMEF, $FEF_{50\%}$, and $FEF_{75\%}$ were significantly lower in the obese with OSA group compared to the obese without OSA group (all $P < .05$). No other differences in PFTs variables between the 2 groups were observed ($P > .05$).

Maximum Inspiratory Pressure (PImax) and Maximal Ventilation Voluntary (MVV)

An absolute value of PImax and MVV of the obese with OSA group were less than those of the controls, but this was not statistically significant ($P = .190$ and $P = .242$) (Table 3).

Table 1. Characteristics of the Obese Children and Adolescents With and Without OSA

Characteristics	Obese With OSA Group (n = 12)	Obese Without OSA Group (n = 12)	*P*
Age (years)	12.08 ± 2.43	12.00 ± 2.73	.938
Gender			
Female	2 (20%)	2 (20%)	n.a
Male	10 (80%)	10 (80%)	n.a
Anthropometric variables			
BW	80.68 ± 21.24	77.57 ± 19.20	.710
Stature	1.61 ± 0.14	1.58 ± 0.12	.653
BMI (kg/m^2)	30.62 ± 3.90	30.57 ± 5.18	.980
BSA	1.83 ± 0.32	1.78 ± 0.27	.685
Skinfold thickness (mm)			
Triceps	31.25 ± 5.91	35.17 ± 5.47	.106
Subscapular	37.00 ± 6.62	39.50 ± 9.13	.451
OSA definition by PSG indexes			
AHI (times/h)	2.07 ± 2.64	N/A	
ODI (times/h)	2.31 ± 1.68	N/A	
SaO_2 nadir (%)	83.17 ± 4.39	N/A	
SRBD score	0.51 ± 0.17	0.23 ± 0.04	.000*

Data are presented as mean ± standard deviation, unless otherwise.
*Significant differences between groups ($P < .05$).
AHI, apnea–hypopnea index; BMI, body mass index; BSA, body surface area; BW, body weight; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PSG, polysomnography; SaO_2nadir, oxygen saturation nadir; SRBD, sleep-related breathing disorder.

DISCUSSION

The results of the present study demonstrated that a significant reduction of MMEF, $FEF_{50\%}$, and $FEF_{75\%}$ were presented in the obese children and adolescents with OSA compared to their peers without OSA. Moreover, the other variables of pulmonary function, including FVC, FVC% predict, FEV1, FEV1/FVC, $FEF_{25\%}$, and PEF, and inspiratory muscle strength and endurance were not different between the 2 groups.

Pulmonary function tests using spirometry is useful for early screening of pulmonary defects.[21] In this study, we found that the values of FEV1/FVC ratio of obese children and adolescents with OSA and their peers without OSA were within the normal range. When compared to the normal-weight children and adolescents of the previous studies,[22,23] the values of FVC and FEV1 in our obese participants with OSA were lower but comparable to those in our obese participants without OSA. A concomitant decrease observed in both FVC and FEV1 and the normal FEV1/FVC ratio could possibly reflect premature closure of small airways in exhalation as mentioned earlier.[24] Additionally, our results found markedly decreased MMEF, $FEF_{50\%}$ and $FEF_{75\%}$ in the OSA group, except for $FEF_{25\%}$. A reduction of $FEF_{25\%-75\%}$ and decreased MMEF at low lung volume has been regarded as early changes in airflow limitation of small airways.[21] Also, there is empirical evidence that $FEF_{75\%}$ is a more sensitive parameter of small airway obstruction than FEV1 and FEV1/FVC ratio in children.[25,26] A study which determined lung volume and respiratory mechanical properties using a plethysmograph and an impulse oscillation system demonstrated that the OSA combined with obesity causes a decrease in lung compliance, which may in turn decrease FRC and increases airflow resistance in total respiratory and peripheral airways in adults.[8] In consistent with the study of Van Eyck et al[3] which found that all pulmonary function variables, especially FRC negatively, correlated with OSA severity.[3] Prior evidence and our findings showed a tendency of flow limitation in obese children and adolescents

Table 2. Pulmonary Function Variables

Pulmonary Function Variables	Obese With OSA Group (n = 12)	Obese Without OSA Group (n = 12)	*P*	Effect Size (*d*)
FVC (L)	2.92 ± 0.77	3.11 ± 0.70	.544	0.26
FVC predict (%)	92.87 ± 20.99	102.44 ± 17.24	.235	0.49
FEV1 (L)	2.48 ± 0.58	2.71 ± 0.59	.344	0.39
FEV1/FVC (%)	85.14 ± 5.57	89.65 ± 6.81	.090	0.72
MMEF (L/s)	2.69 ± 0.59	3.37 ± 0.81	.028*	0.94
$FEF_{25\%}$ (L/s)	4.20 ± 1.03	5.00 ± 1.57	.154	0.58
$FEF_{50\%}$ (L/s)	2.96 ± 0.72	3.71 ± 0.88	.031*	0.92
$FEF_{75\%}$ (L/s)	1.38 ± 0.31	2.00 ± 0.64	.006*	1.12
PEF (L/s*)	4.65 ± 1.11	5.20 ± 1.57	.329	0.39

Data are presented as mean ± standard deviation.
*Significant differences between groups ($P < .05$).
BMI, body mass index; BSA, body surface area; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FVC% predict, forced vital capacity percent predict; $FEF_{25\%}$, forced expiratory flow at 25% of the vital capacity; $FEF_{50\%}$, forced expiratory flow at 50% of the vital capacity; $FEF_{75\%}$, forced expiratory flow at 75% of the vital capacity; PEF, peak expiratory flow; MMEF, maximal mid-expiratory flow.

Table 3. The Absolute Values of Respiratory Muscle Function

Respiratory Muscle Function	Obese With OSA Group (n = 12)	Obese Without OSA Group (n = 12)	*P*	Effect Size (*d*)
PImax (cmH_2O)	2.55 ± 0.83	3.12 ± 1.18	.188	0.54
MVV (L/min)	78.42 ± 26.95	92.17 ± 29.00	.242	0.49

BMI, body mass index; BSA, body surface area; MVV, maximal voluntary ventilation; PImax, maximal inspiratory pressure.

with OSA; however, PFT used in this study is not the standard to evaluate small airway disease. Additionally, MMEF and flow toward the end of the forced expiratory maneuver have been reported that limit their sensitivity for detecting small airway disease in individual patients.[27,28] Therefore, further research is warranted before a clear conclusion can be drawn.

When analyzing the inspiratory muscle function, we also maintain that, although the inspiratory muscle strength and endurance in obese with OSA were lower than in those without OSA, no statistical difference was found. At the same age, the average PImax value of obese children with OSA in this study was similar to those of severe obese children that were tested in a previous study[29] and was inferior to those of normal-weight subjects.[30] Taken together, it is possible that the observed inspiratory muscle defect might be caused by the mechanical stress of obesity upon the respiratory system[6] as mentioned earlier, rather than OSA.

This study has some strength and limitations. To eliminate the confounding factors such as age, gender, and BMI, the protocol used in this study was performed by matches between OSA and non-OSA participants. Besides the limited availability and accessibility to PSG or even a mobile sleep machine, it's not a routine practice for children with obesity to use these tools for diagnosis of OSA. In this study, performing a portable sleep machine for participants with no OSA was felt to be impractical as did the OSA group. Instead, the SRBD-PSQ which have moderate accuracy for predicting OSA[14] was used to classify the OSA and non-OSA participants. As a result, false-positive or false-negative results for group classification could possibly happen and, in turn, affect the reliable of the main outcomes. Another limitation was the sensitivity of the portable sleeping tool which has been shown to be inferior to the standard PSG for diagnosis of OSA that might lead to underestimating or overestimating OSA severity.[31] Lastly, a cross-sectional study in small groups limits the ability to draw a causal relationship between pulmonary and respiratory muscle function in obese with OSA participants. Therefore, further studies using larger sample sizes and other parameters such as TLC, FRC, and RV are required to confirm our findings.

CONCLUSION

Obstructive sleep apnea did not modify pulmonary and respiratory muscle function in obese children and adolescents. Moreover, the observed reduction in MMEF and flow towards the end of the forced expiratory maneuver should be warranted using a standardized test.

Ethics Committee Approval: This study was approved by Ethics committee of the Faculty of Associated Medical Sciences, Chiang Mai University, (Approval No: XXXXXX).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.P., N.S., S.C.1, S.C.2, K.A., ; Design – S.P., S.C.1, S.C.2, K.A.; Supervision – S.P., N.S.; Resources – S.P., ; Materials – P.S., K.W.; Data Collection and/or Processing –N.S., S.C.1, S.C.2, K.A., P.S., , K.W.; Analysis and/or Interpretation – S.P., N.S., S.C.1, S.C.2, K.A., P.S., K.W.; Literature Search – S.P., S.C.1, S.C.2, K.A., P.S., K.W., ; Writing Manuscript – S.P., S.C.1, S.C.2, K.A., P.S., K.W.; Critical Review – S.P., N.S., S.C.1, S.C.2, K.A.

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Original Article

The Impact of Mechanical Ventilation Modes on Complications of Fiberoptic Bronchoscopy in Critically Ill Patients

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Abstract

OBJECTIVE: The effects of fiberoptic bronchoscopy are not elucidated in different mechanical ventilation modes. The present study aimed to evaluate the effects of fiberoptic bronchoscopy on lung mechanics, ventilation parameters, and gas exchange in 2 often-used modes, volume control and pressure control, in invasively ventilated patients followed up in the intensive care unit.

MATERIAL AND METHODS: Eligible patients were screened and included in the study after intensive care unit-fiberoptic bronchoscopy database search. Patients who underwent fiberoptic bronchoscopy under volume control and pressure control mechanical ventilation modes were compared. The primary outcome was the occurrence of any complication within the first 24 hours after the procedure, and secondary outcomes were changes in lung mechanics (dynamic lung compliance and airway resistance) and gas exchange (arterial partial pressures of oxygen and carbon dioxide).

RESULTS: A total of 61 patients (median age: 69 years, 60.7% male) were included. Twenty-nine (47.5%) patients were ventilated in volume control mode and 32 (52.5%) in pressure control mode during the fiberoptic bronchoscopy procedure, and the median (interquartile range) duration of the procedure was 9 [8-11] minutes. Baseline dynamic lung compliance, airway resistance, arterial partial pressures of oxygen and carbon dioxide, and the fraction of inspired O_2 were similar in both groups. After fiberoptic bronchoscopy, dynamic lung compliance decreased in both groups, and airway resistance and peak airway pressures increased but reached pre-fiberoptic bronchoscopy values at the 1st hour after the procedure. No significant differences were detected in both groups in terms of blood gas values and lung mechanics in the 1st and 24th hours after the procedure. In both groups, the 24th hour fraction of inspired O_2 was the same as the pre-fiberoptic bronchoscopy values, but the ratio of arterial partial pressure of oxygen and the fraction of inspired O_2 improved. No complications developed in patients within 24 hours after the procedure.

CONCLUSION: No differences were detected in terms of gas exchange and pulmonary mechanics, and complications in volume control and pressure control modes in critically ill intubated patients.

KEYWORDS: Fiberoptic bronchoscopy, mechanical ventilation, intensive care, mode
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INTRODUCTION

Fiberoptic bronchoscopy (FB) is increasingly used in intensive care units (ICU) for both diagnostic and therapeutic purposes because of its ease, bedside applicability, and low complication rates.[1] Fiberoptic bronchoscopy under mechanical ventilation (MV) in invasively ventilated critically ill patients has a relatively good safety profile even though it has several physiological complications, such as increased airway resistance (R_{aw}), hypoxemia, and hypercapnia.[2,3] While performing FB through the endotracheal tube (ETT), peak inspiratory pressure (PIP) and alveolar pressure may increase and affect many ventilation parameters, such as tidal volume (VT) flow rate and dynamic lung compliance (C_{dyn}). Moreover, during bronchoalveolar lavage (BAL), aspiration causes more deepened hypoxemia and decreases the end-expiratory lung volume and lung compliance, especially in patients with severe hypoxemia.[4] For this reason, it is necessary to think of proper MV settings before and during FB and consider setting readjustments in case needed.

Fiberoptic bronchoscopy can be performed in many MV modes depending on the patient's characteristics and needs. Volume control (VC) mode is the most used mode as it maintains VT and therefore minute ventilation. Another option is pressure control (PC) mode which is used very often in critically ill patients when there is the risk for high airway pressures. However, it is used to a lesser extent because of the high risk of decreased minute ventilation due to increased R_{aw}.

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Currently, there are no evidence-based recommendations for mode selection during FB procedure in invasively ventilated critically ill patients. Expert opinion is to perform FB in VC mode and with a possibility of reduced VT and allowing permissive hypercapnia.[1] In our center, we often perform FB for diagnostic and therapeutic purposes and our general approach is not to change MV mode while performing FB whenever possible. Our clinical observation was there was no superiority of VC mode over PC mode for early and late FB complications. Therefore, to test our hypothesis, we conducted the present study. The primary outcome was the occurrence of any hypoxemic complications within the first 24 hours after the FB procedure in invasively ventilated patients, and secondary outcomes were changes on lung mechanics (C_{dyn}–R_{aw}) and gas exchange (arterial partial pressures of oxygen [PaO_2] and carbon dioxide [$PaCO_2$])

MATERIAL AND METHODS

Study Population

This retrospective study was performed in adult ICU after the Dokuz Eylül University ethics committee approval (No. 2020/06-29). Intensive care unit-fiberoptic bronchoscopy (ICU-FB) database was screened for adult (≥18 years) patients who underwent FB and invasively ventilated either with VC or PC modes. Informed consent was waived because of the nature of the study.

Fiberoptic Bronchoscopy Procedure

Indication and the decision for FB were primarily determined by consulting intensivists. The study team had no contribution to the decision on making an FB indication. All procedures were performed by 1 intensivist–pulmonologist who had expertise in performing FB in critically ill patients of >15 years. According to local ICU-FB protocol, severe hemodynamic instability and bleeding diathesis were considered as the main contraindications to performing FB [1]. All patients were monitored for vital signs (electrocardiography, pulse oximetry, and blood pressure) during and after the procedure.

Variables

The demographic data of patients (age, gender, main reason for ICU admission, and reason for FB), Acute Physiology and Chronic Health Evaluation [APACHE] II score, Glasgow Coma Scale (GCS) score, Sequential Organ Failure Assessment (SOFA) score, and clinical characteristics (duration of MV, need for vasopressor therapy, and renal replacement therapy) were recorded. Patients were divided into 2 groups according to the ventilation modes as follows: the VC and PC groups.

MAIN POINTS

- Fiberoptic bronchoscopy (FB) is frequently used in practice in mechanical ventilation patients.
- The effects of mechanical ventilation modes on lung mechanics and frequency of complications during FB are not clear yet.
- Expert opinions suggest that adequate ventilation should be provided during the procedure and volume control (VC) mode should be preferred.
- In our study, no significant differences were found between the pressure control and VC modes, which are frequently used clinically during and after FB.
- Broad-based studies including other mechanical ventilation modes are needed.

Mechanical Ventilation Settings

All patients were ventilated with Dräger Evita Infinity V500 (Dräger Medical GmbH; Lübeck, Schleswig-Holstein, Germany) series ventilators. Ventilator settings were set by the primary consulting intensivist and were kept constant during FB except for fraction of inspired oxygen (FiO_2).

Usual ventilatory settings for VC mode were an average of 5-6 cmH_2O for positive end-expiratory pressure (PEEP), VT of 5-8 mL/predicted body weight, inspiration/expiration ratio of 1/2-3, and PIP alarm limit of 40 cmH_2O. For PC mode, inspiratory pressure was adjusted to VT calculated and lower alarm limit for minute ventilation was set to <4 L/min.

The ICU sedation protocol consisted of midazolam and fentanyl/remifentanil infusion before and during the procedure according to the depth of sedation that allows spontaneous breathing of patients as much as possible.

After the confirmation of ETT diameter to be >8.0 mm in the bronchoscope (5.9-mm outer-diameter Olympus BF 10 bronchoscope [Olympus, Tokyo, Japan]) was placed in ETT with a special adapter valve. For preoxygenation, 5-10 minutes before the procedure, FiO_2 was set at 0.9-1.0 and was kept in this setting throughout the procedure. All ventilator parameters set by the consulting intensivist were kept stable, and the inhaled and exhaled VTs and vital findings during the procedure were monitored and recorded closely. The duration of FB, the amount of fluid given and recovered for bronchial lavage, and BAL were noted. FiO_2 was decreased gradually to guarantee peripheral (pulse) oxygen saturation (SpO_2) >90% after FB. After FB procedure and at 1st and 24th hours, patients' vital signs (i.e., heart rate [HR], mean arterial pressure [MAP], and respiratory rate [RR]), arterial blood gas values, mechanical ventilator parameters, pulmonary mechanics, and PaO_2/FiO_2 values were recorded. Possible complications in the first 24 hours after FB, FB-related desaturation (SpO_2 <90), hemodynamic deterioration, barotrauma-related complications such as pneumothorax and/or pneumomediastinum, and bleeding were recorded.

Arterial blood gas values (PaO_2, $PaCO_2$), oxygen saturation (SaO_2) mechanical ventilator settings for PEEP, PIP, VT, FiO_2, C_{dyn}, and R_{aw} at the end of the procedure, for the 1st and 24th hours, were recorded (formula: C_{dyn} (mL/cmH_2O) = *VT* (mL)/[*PIP* (cmH_2O) − *PEEP* (cmH_2O)]. Airway resistance was measured with 40 L/min square by using the following formula: R_{aw} (cmH_2O/L/s) = [*Peak inspiratory pressure* (cmH_2O) − *plateau pressure* (cmH_2O)]/*final inspiratory flow* (L/s).

Statistical Analysis

Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as the median and interquartile range. Categorical variables between groups were compared with chi-square or Fisher's exact test, continuous variables were compared with Mann–Whitney *U* test. Pre- and post-FB values for compliance and resistance

and arterial blood gas values were compared with Student's *t*-test. A 2-tailed *P*-value of <.05 was considered statistically significant. Statistical analysis was performed with Statistical Package for the Social Sciences version 26.0 (IBM Corporation, Armonk, NY, USA) program.

Clinic Characteristics and Outcomes of Patients

Of 61 patients (median age 69 years [61-69] and 37 [60.7%] of them being male), 32 (52.5%) underwent FB in PC mode and 29 (47.5%) in VC mode.

Patients in the VC group were older than the PC group, but the age did not significantly differ between the groups (77 [70-83] vs. 67 [63-76], respectively, *P* = .09). In the VC group, the median APACHE II value (24 [21-30] vs. 22 [18-26], respectively, *P* = .14), SOFA score (8 [5-8] vs. 6 [5-7], respectively, *P* = .08), and GCS (9 [7-11] vs. 8 [6-10], respectively, *P* = .36) were higher than the PC group; these parameters did not significantly differ between the groups. The main reasons for the ICU admission were respiratory failure (41%), sepsis/septic shock (18%), neurological disease (18%), postoperative (14.85), and trauma (8.2%). The reasons for the ICU admission did not significantly differ between the groups. The indications for the FB did not particularly differ between the groups (Table 1).

On the day of FB procedure, the number of patients who needed vasopressors (14 [43.8%] vs. 10 [37.9%], respectively, *P* = .60), who were diagnosed with acute kidney injury (16 [50.0%] vs. 12 [41.4%], respectively, *P* = .60), and who underwent hemodialysis (6 [18.7%] vs. 2 [6.9%], respectively, *P* = .26) did not statistically differ between the groups.

The duration of invasive MV (20 [10-36] vs. 12 [9-28], respectively, *P* = .33), the length of ICU stay (22 [18-28] vs. 18 [15-32], respectively, *P* = .39), hospital mortality (23 [79.3%] vs. 19 [59.4%], respectively, *P* = .10), and ICU mortality (20 [68.9%] vs. 18 [56.3%], respectively, *P* = .42) were not statistically significant between the VC group and the PC group.

Median FB duration was similar in both groups, [10 min (8-13) for PC group vs. 9 min (8-10) for VC group; *P* = .11]. The amount of NaCl 0.09% used during bronchial washings [87 mL (50-100) for PC group and 80 mL (40-100) for VC group, (*P* = .47)] and recovered amounts [45 mL (35-65) for

Table 1. Baseline Characteristics of the Patients

Basic Variables	All Patients (n = 61)	PC Mode (n = 32)	VC Mode (n = 29)	*P*
Age	69 (61-79)	67 (63-76)	77 (70–83)	.09
Male sex	37 (60.7)	19 (51.4)	18 (62.1)	1.00
Apache II score	23 (19-29)	22 (18-26)	24 (21-30)	.14
SOFA[a] score	6 (5-8)	6 (5-7)	8 (5-9)	.08
GCS score	8 (7-11)	8 (6-10)	9 (7-11)	.36
Main reason for ICU admission				
Sepsis/septic shock	11 (18.0)	5 (15.6)	6 (20.7)	.74
Respiratory failure	25 (41.0)	14 (43.8)	11 (37.9)	.79
Postoperative	9 (14.8)	5 (15.6)	4 (13.8)	1.00
Neurological disease	11 (18.0)	5 (15.6)	6 (20.7)	.74
Trauma	5 (8.2)	3 (9.4)	2 (6.9)	1.00
Indications for FB				
Pneumonia	31 (50.8)	15 (46.8)	16 (55.2)	.54
Atelectasis	8 (13.1)	4 (12.5)	4 (13.8)	1.00
Hemoptysis	5 (8.2)	2 (6.3)	3 (10.3)	.66
Airway exploration	17 (27.9)	11 (34.4)	6 (20.7)	.26
Event on FB day				
Vasopressor need[b]	24 (39.3)	14 (43.8)	10 (37.9)	.60
AKI	28 (45.9)	16 (50.0)	12 (41.4)	.60
HD need	8 (13.1)	6 (18.7)	2 (6.9)	.26
Invasive MV duration (days)	14 (9-32)	12 (9-28)	20 (10-36)	.33
ICU length of stay (days)	20 (15-29)	18 (15-32)	22 (18-28)	.39
ICU mortality	38 (62.3)	18 (56.3)	20 (68.9)	.42
Hospital mortality	42 (68.9)	19 (59.4)	23 (79.3)	.10

All values are expressed as numbers (percentages) or median (interquartile range).
[a]SOFA score in the first day; [b]norepinephrine >0.15 µg/kg/min.
APACHE, Acute Physiology And Chronic Health Evaluation Scale; AKI, acute kidney injury; FB, fiberoptic bronchoscopy; GCS, Glasgow Coma Scale; HD, hemodialysis; PC, pressure control; MV, mechanical ventilation; SOFA, Sequential Organ Failure Assessment Scale; VC, volume control.

PC group and 40 mL (23-53) for VC group (P = .16)] were similar in both groups and did not reach a statistical significance.

No complications occurred during the FB procedure and in the next 24 hours.

Vital Signs, Lung Mechanics, Blood Gas, and Mechanical Ventilator Data

The vital parameters such as MAP, HR, RR were not significantly different between the groups before FB. Before the FB, the median FiO_2 value were higher in the VC group than the PC group (45% [40-52] vs. 40% [35-47] , respectively, P = .23) as well as the median SaO_2 (98% [95-98] vs. 96% [93-98], P = .41), PaO_2 (91 mmHg [78-110] vs. 85 mmHg [76-111], respectively, P = .68), and PaO_2/FiO_2 ratio (231 [178-254] vs. 203 [158-225], respectively, P = .12) were higher in the PC group than the VC group. All blood gas analysis values presented above were not statistically different between the groups.

Before the FB, the median VT (482 [421-581] vs. 450 [416-484] mL, respectively, P = .09) was higher in the PC group than the VC group, as well as, the median PIP (26 cmH_2O [21-29] vs. 23 cmH_2O [22-27], respectively, P = .36) was higher in the VC group than the PC group. The median PEEP value was similar between the groups (6 cmH_2O [5-7] vs. 6 cmH_2O [5-8], respectively, P = .50). The median value of C_{dyn}, R_{aw}, and the mechanical ventilator paramaters before the FB were not statistically significant between the groups. It was observed that median C_{dyn} was lower in the VC mode group than in the PC group immediately after FB (25.5 mL/cmH_2O [22.0-33.0] and 34.0 mL/cmH_2O [24.5-45.5], respectively); however, it did not reach a statistical significance (P = .06). It was observed that PIP increased immediately after FB was similar in both groups (delta pressure was 2.0 cmH_2O for PC and VC modes, P = .27). C_{dyn}, R_{aw}, and PIP reached similar values to baseline at the 1st hour after the procedure and kept constant till 24th hour (Table 2).

DISCUSSION

Currently, there are no clear evidence-based recommendations for MV mode selection during FB in invasively ventilated patients. In the current study, we aimed to investigate the effects of FB in the most commonly used MV modes in clinical practice. We found that FB can be performed safely without changing ventilatory settings. Second, FB induced similar but clinically non-significant changes in respiratory mechanics and gas exchange in both PC and VC modes.

In our study, we have kept all MV settings unchanged except for FiO_2 during FB. Fiberoptic bronchoscopy-related gas exchange abnormalities emerge at different rates in almost all critical patients. Fiberoptic bronchoscopy may cause up to a 30% decrease in oxygenation; this usually returns to the values before the procedure within 2 hours.[3] It was reported that there is a decrease of 4-38 mmHg (average 20 mmHg) in PaO_2 during FB.[5] The reason for this may be the intrapulmonary shunt formation, development of ventilation/perfusion disorder because of lavage fluid, and bronchospasm that is secondary to tracheal stimulation.[6] To prevent hypoxemia, we have preoxygenated patients and used FiO_2 to 0.9-1.0 throughout the procedure. We believe that this was a successful approach in this cohort as none of the patients had any desaturation attacks and all FB procedures were performed without any interruption.

The optimal ventilation strategy during FB is still questionable. In a previous study, Meduri and Chastre[7] proposed a volume targeted ventilation strategy in which the ventilator is set to ensure adequate ventilation during FB for stable VT and therefore minute ventilation. However, they also noted that hyperinflation, barotrauma, pneumothorax, and hemodynamic deterioration due to expiratory flow limitation may occur and this may be dangerous, especially in patients with high PEEP need. An option to decrease the risk for barotrauma would be decreasing the PEEP level by 50%.[1] In our study, we observed that there was a slight decrease in VT and an insignificant increase in $PaCO_2$. However, both changes were clinically insignificant.

In this study, it was observed that FB was performed mostly for microbiological sampling for pneumonia and airway assessment including atelectasis. For that reason, only bronchial lavage was performed and we have avoided BAL due to the risks mentioned above. This approach might lead to non-significant differences in C_{dyn} and R_{aw} in both groups. The saline, which is not retrieved for bronchial lavage, might decrease the VT and worsen gas exchange because of increased ventilation–perfusion incompatibility.[8,9] Moreover, the lavage fluid might also cause inflammatory pulmonary edema inactivation of surfactant and may result in atelectasis and changes in respiratory mechanics.[10] Chou et al[11] showed that R_{aw} increased approximately up to 22% and C_{dyn} decreased 14% immediately after BAL. Klein et al[12] examined the post-BAL changes in 18 patients in MV and reported that there was a temporary increase in pulmonary resistance and a 20% decrease in compliance 8 minutes after the procedure. They also emphasized that compliance approached the initial values 3 hours after the procedure. These studies did not present the possible effects of any MV mode during FB.

İn our study, no complications were encountered in our patient group. Although FB is considered to be a safe procedure, the general complication rates vary between 4% and 10% in intensive care patients.[13,14] Complications may be related to patient characteristics (i.e., age, presence/degree of hypoxemia, comorbidities, and clotting abnormalities), procedural factors (i.e., the duration, sedation, and type of the procedure), and the experience of the operatör.[15] The most common complications are bronchospasm, hypoxemia, cardiac arrhythmias, hypotension, bleeding and hemoptysis, pneumothorax, myocardial infarction/pulmonary edema, and mortality.[16] Complications such as pneumothorax and subcutaneous emphysema can occur immediately after FB or after some time. This may be especially important for patients receiving MV support in ICU, and patients must be monitored for such delayed complications in the first 24 hours after the procedure.[16] We believe that the absence of any complications in our cohort is due to our center's expertise in FB. Another reason for the lower complication rate might be due to short procedural time. The median bronchoscopy duration in both MV modes was 9 minutes in our study and was lesser than generally reported in the literature.[17,18]

Table 2. Vital Signs, Lung Mechanics, Blood Gas Analysis, and Mechanical Ventilator Data Before FB, Immediately After FB, and on the 1st and 24th Hours After FB

	Before FB			Immediately After FB			After FB 1st Hour			After FB 24th Hour		
Variables	**PC Mode**	**VC Mode**	***P***	**PC Mode**	**VC Mode**	***P***	**PC Mode**	**VC Mode**	***P***	**PC Mode**	**VC Mode**	***P***
Vital signs												
MAP (mmHg)	72 (65-77)	70(68-75)	.22	75 (69-88)	72 (70-78)	.30	78 (71-82)	75 (73-82)	.22	75 (70-79)	72 (68-73)	.24
HR (/min)	90 (86-111)	95 (91-115)	.29	90 (74-113)	102 (95-118)	.28	97 (88-111)	96 (65-112)	.36	102 (92-112)	99 (86-108)	.18
RR (/min)	16 (145-22)	18 (16-19)	.31	18 (16-23)	20 (15-24)	.56	18 (15-24)	20 (16-24)	.23	18 (16-22)	23 (18-25)	.11
Arterial blood gas analysis												
pH	7.39 (7.32-7.43)	7.39 (7.34-7.43)	.88	7.36 (7.28-7.45)	7.34 (7.29-7.41)	.63	7.39 (7.30-7.44)	7.41 (7.31-7.41)	.77	7.39 (7.30-7.44)	7.41 (7.35-7.43)	.27
PaO_2 (mmHg)	91 (78-110)	85 (76-111)	.68	90 (74-161)	105 (83-208)	.09	92 (76-107)	85 (76-98)	.59	96 (77-113)	86 (81-104)	.37
$PaCO_2$ (mmHg)	41 (38-48)	45 (38-51)	.50	43 (38-49)	46 (39-54)	.12	43 (36-47)	46 (35-52)	.48	43 (38-48)	45 (35-52)	.68
SaO_2 (%)	98 (95-98)	96(93-98)	.41	98 (95-99)	99 (96-99)	.27	97 (95-98)	97 (95-98)	.47	98 (95-99)	97 (96-99)	.51
FiO_2 (%)	40 (35-47)	45 (40-52)	.23	50 (40-80)	80 (50-1.00)	.07	40 (35-50)	45 (40-50)	.37	40 (30-50)	45 (40-50)	.32
PaO_2/FiO_2	231 (178-254)	203 (158-225)	.12	200 (150-246)	205 (91-236)	.38	205 (150-268)	185 (150-240)	.26	240 (181-265)	211 (116-252)	.20
Mechanical ventilator data												
TV (mL)	482 (421-581)	450 (416-484)	.09	470 (440-553)	441 (411-480)	.28	475 (460-560)	450 (421-480)	.18	490 (431-550)	450 (401-557)	.27
PEEP (cmH_2O)	6 (5-7)	6 (5-8)	.50	6 (5-7)	6 (5-8)	.36	6 (5-7)	6 (5-8)	.36	6 (5-7)	6 (5-8)	.36
PIP (cmH_2O)	23 (22-27)	26 (21-29)	.36	25 (22-29)	28 (24-29)	.27	26 (23-31)	26 (23-30)	.96	23 (20-26)	24 (19-29)	.73
Lung mechanics												
C_{dyn} (mL/cmH_2O)	36 (27-50)	29 (23-43)	.33	34 (25-46)	26 (22-33)	.06	38 (26-41)	29 (23-41)	.17	36 (30-55)	31 (26-47)	.26
R_{aw} ($cmH_2O/L/s$)	12 (11-14)	13 (10-15)	.53	14 (10-17)	15 (12-18)	.26	14 (11-17)	14 (12-16)	.77	12 (11-16)	12 (8-17)	1.00

All values are expressed as median (interquartile range).
C_{dyn}, dynamic lung compliance; FiO_2, fraction of inspired oxygen; HCO_3, bicarbonate; HR, heart rate; MAP, mean arterial pressure; PaO_2, arterial partial oxygen pressure; $PaCO_2$, arterial partial carbon dioxide pressure; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; R_{aw}, airway resistance; RR, respiratory rate; SO_2, oxygen saturation; TV, tidal volume.

There are several limitations of this study. The most important limitation of our study was the limited number of patients and our results are preliminary. Moreover, the results cannot be generalized since the study provided single-center data. The second limitation is we only had evaluated the risk of FB and bronchial washing procedure; therefore, the risks of other interventions, such as BAL and transbronchial biopsy, were not evaluated. On the other hand, our study has some strengths. First, there are limited studies conducted in the literature to assess MV modes during FB in critically ill patients. Second, we think that our protocol of increasing FiO_2 and keeping MV settings unchanged during FB is a successful and much easy approach that can easily be used in clinical practice.

CONCLUSION

Fiberoptic bronchoscopy is an essential tool for diagnostic and therapeutic purposes in the ICU. However, FB in intubated, critically ill patients needs specific considerations as they are more prone to developing complications. So far, there is limited data for how to ventilate patients during FB. Usually, to sustain adequate ventilation, VC mode is recommended. However, our preliminary findings suggest that ventilatory modes do not affect the development of complications and neither have superiority over another. More studies are needed to understand the optimal ventilation strategy during FB in critically ill patients.

Ethics Committee Approval: This study was approved by Ethics committee of Dokuz Eylül University, (Approval No: 2020/6-29).

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Original Article

Effects of Education on Care Burden and Quality of Life to Caregivers of Patients with COPD

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Abstract

OBJECTIVE: This research was carried out in a single group, pretest–post-test design in order to determine the effect of education on care burden and life quality of caregivers provided to caregivers of patients diagnosed with chronic obstructive pulmonary disease who received healthcare at their home.

MATERIAL AND METHODS: The population of the study was composed of 35 patients with chronic obstructive pulmonary disease living in the city center and receiving home health care and the caregivers of these patients. Research data were obtained by using the Caregiver Information Form, Patient Information Form, Caregiver Burden Inventory, and World Health Organization Quality of Scale-Bref Quality of Life Scale. Caregivers' burden and quality of life were reevaluated once after every 1 month and 3 months following the education.

RESULTS: It was determined that caregivers were the spouses and children of the patients, the majority of them did not consider themselves sufficient in providing care; their care burden was high and their quality of life was low. In post-education follow-ups, a significant reduction in caregiver burden and a significant increase in quality of life were detected.

CONCLUSION: The education prepared considering the learning needs was seen to be effective in reducing the care burden of caregivers of patients with chronic obstructive pulmonary disease and in improving their quality of life.

KEYWORDS: COPD, caregiver, care burden, quality of life, home health care
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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the chronic diseases that causes an increased economic and social burden due to high care and treatment expenditures.[1-3] In the global disease burden study report, it is stated that there were 251 million COPD patients worldwide in 2016, and 3.17 million deaths that occurred globally in 2015 were related to COPD.[4] The burden of COPD on the families and country economy reaches significant dimensions with the economic losses arising from diagnosis, treatment expenditures, early deaths, and loss of labor force.[5]

Patients with COPD, who experience significant functional losses during the disease process, need the help and support of a caregiver in many areas.[6,7] This situation requires care services to move from hospital to home care services, and the need for informal caregivers is increasing.[8] The caregivers of patients with COPD assume many important responsibilities for taking care of patients in the home environment. However, it is a known fact that the majority of caregivers do not have sufficient knowledge. Although caregivers' living with COPD patients in the same home environment is positive in terms of continuity and effectiveness of care, this situation has a restrictive effect on caregiver's own activities.[9] In a study by Kanervisto et al.[10] 37% of patients with COPD stated that the disease affected them negatively, while 55% of caregivers of the same patients reported that their responsibility to provide care negatively affected their own lives. Nakken et al[11] emphasize that it is important to investigate the interaction between patients and caregivers and to take the needs of caregivers into account. In a study by Miravitlles et al.[12] it was revealed that 35% of caregivers had health problems, 83% had problems related to leisure/social activities, and 38% had problems in fulfilling their professional responsibilities due to caregiving; these problems increased in relation to the degree of dependence of the patient receiving care. It has been reported that caregivers, who report that they are affected and need help in providing care, have a higher burden of care[13] and their quality of life decreases as the care burden increases.[14] Marques et al[15] reported that the inclusion of caregivers of patients with COPD in a multidisciplinary pulmonary rehabilitation program contributed to caregivers' developing strategies to cope with stress and psychosocial adjustment.

As the severity of the disease increases, the responsibilities of the caregivers of patients with COPD become more and more complex. In addition to providing care to patients, caregivers should support them as well.[16] This situation increases the learning needs of the caregivers of patients with COPD regarding the disease and care. Health professionals and health

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systems actively identify caregivers[17] and determine and support caregivers' needs are of great importance for both caregivers and the patient they care for.[16]

The fact that chronic disease management is not sufficient is one of the most important reasons for increasing the economic burden and care burden of diseases. Informal caregivers are one of the most important sources of support who support patients' disease management skills. For this reason, health systems should contain elements that reduce the cost of care of patients, ensure that they achieve optimum quality of life, and support caregivers who take on the responsibility of home care. Professional support provided to caregivers will make an important contribution to providing a better quality of care to patients and reducing the burden of care.

MATERIAL AND METHODS

This research was carried out in a single group, pretest–post-test design with the purpose of determining the effect of training on caregiver burden and life quality provided to caregivers of patients diagnosed with COPD who received healthcare at their home.

According to the records of the Home Health Service Coordination Center, the population of this research was composed of 35 COPD patients living in the city center and receiving home health care and caregivers who took care of these patients. The sample of this study was formed by 35 adult caregivers living in a provincial center who had been taking care of the patient for at least 6 months, who are primarily responsible for the care of the patient, who speak Turkish, who are literate, who do not have any cognitive and sensory problems preventing communication, and who do not have a diagnosed psychiatric disease.

Data collection tools: In the collection of research data, Caregiver Information Form, Patient Information Form, Caregiver Burden Inventory (CBI), and World Health Organization Quality of Scale (WHOQOL)-Bref Quality of Life Scale were used.

Caregiver Information Form: Caregiver Information Form consists of 12 questions. In the form, there are questions to determine the socio-demographic characteristics (age, gender, marital status, etc.) of caregivers, responsibilities of the caregiver, the conditions of being affected by being a caregiver, and caregivers' information requirements about caregiving.

Patient Information Form: Patient Information Form consists of 14 questions. In this form, there are questions determining the socio-demographic characteristics of patients (age, gender, education level, marital status, family type, occupation, employment status, social security, smoking and alcohol use status, source of income, etc.) and patient characteristics regarding COPD (duration of COPD, COPD stage, hospitalization and applying to the emergency service due to COPD in the recent year, the severity of dyspnea, concomitant health problems, the use of oxygen at home, the medications used, and the use of non-drug complementary treatment).

WHOQOL-Bref Quality of Life Scale: The scale developed by the World Health Organization contains 26 questions by which the general perception of quality of life is questioned. A 5-point Likert scale is used in the scale. The Turkish validity and reliability study of the scale was performed by Eser et al.[18] The WHOQOL-Bref-TR version with a national question added in the Turkish validity study of the scale consists of 27 questions. The high score obtained from the scale indicates that the quality of life is high. Cronbach's alpha coefficient of WHOQOL-Bref Quality of Life Scale was determined as 0.85.

Caregiver Burden Inventory: It is a 5-point Likert type measurement tool with 24 statements developed by Novak and Guest[19] to measure the effect of caregiving on caregivers' relatives. Based on the view that caregivers' burden is multi-dimensional, it consists of 5 sub-dimensions (time-dependency burden, developmental burden, physical burden, social burden, and emotional burden). Physical burden includes 4 items, other sub-dimensions contain 5 items. The total score that can be obtained from the scale varies between 0 and 100. The high score shows a high degree of care burden. Adaptation of the inventory to Turkish society was performed by Kucukguclu et al.[20] In the study, Cronbach's alpha coefficient of the inventory was calculated as 0.76.

Application of the Research: The records of the COPD patients who receive home healthcare services were taken from the records of the Provincial Health Directorate Home Health Services Coordinators of the province where the study was conducted. The researcher visited all the patients with COPD (35 patients), who are registered at the Home Health Services Coordinators, and their caregivers in their homes. Informed consent was obtained from caregivers, who agreed to participate in the study, by explaining the research to them and their patients. All patients and caregivers interviewed agreed to participate in the study. In the first interview, the Patient Information Form, Caregiver Description Form, WHOQL-Bref Quality of Life Scale, and CBI were applied to the patients and their caregivers who accepted to participate in the study. The learning needs of caregivers were determined in line with the obtained data. The "Caregiver Training" content was created with the aim of meeting the learning needs of caregivers.

Training groups consisting of 10-11 caregivers were formed. All the training was held by the researcher at the Home Health Services Coordinators building in the caregiver information class prepared for this training. The training was provided to the caregivers on the function of the respiratory system, the causes of COPD, drug therapy, chest physiotherapy practices, the effects of the disease on daily life, what to do to identify the symptoms of the disease, and the importance of regular follow-up in line with the previously defined learning needs of caregivers. The caregivers attended the training session in the caregiver information class once a week. The training was carried out in 2 sessions. During the training sessions, lectures, questions and answers, demonstration techniques, and visual training materials were shown by means of a projector. The demonstration method was preferred in order for the caregivers to comprehend some applications well. With the demonstration method, caregivers' training was supported by performing applications such as oxygen therapy (nasal cannula and oxygen application with a facial mask),

nebulizer, inhaler, and bronchodilator medication. In order to encourage the active participation of caregivers and reinforce their learning, examples were provided based on short stories of patient and case examples in accordance with the content. Caregivers were encouraged to ask questions. At the end of each session, all participants were given written training material and telephone numbers to reach the researcher whenever they wanted to get information.

Three caregivers could not attend the training sessions because there was no one else to take care of their patients and left the study. The research was completed with 32 caregivers. The WHOQOL Bref Quality of Life Scale and the CBI were re-applied to the caregivers after every 1 month and 3 months.

Data Analysis: Data of the study were analyzed with Statistical Package for Social Sciences 23.0 (IBM SPSS Corp.; Armonk, NY, USA) package program. Frequency distributions were used for categorical variables, and descriptive statistics were used for numerical variables. The data compliance status with the normality assumption was determined by the Shapiro–Wilk normality test. Parametric tests were used for comparisons of the data that met the normality assumption. Pearson's correlation coefficient was used in the determination of the degree of noncausal relationships between 2 numerical variables, Student's *t*-test was employed in evaluating the difference between the 2 groups, and the difference between more than 2 dependent groups was evaluated by repeated measures analysis of variance. The level of significance was set at $P < .05$.

Ethical Aspect of the Research: Written permission from the Provincial Health Directorate was obtained for the research and the ethics committee approval was received from the Ethics Committee Presidency (Decision No. 2018-12/06, dated: December 5, 2015). Each stage of the research was carried out in accordance with ethical principles.

Findings

The average age of patients with COPD participating in the study was 79.88 ± 11.07 years, and more than half were male, literate, and single. It was determined that the majority of the patients had nuclear families, none of them were working, more than half of them had a diagnosis of COPD for 5 years and less, and most of them had 3 or more hospitalizations in the recent year and repeated application to the emergency room due to exacerbation of COPD. It was determined that approximately 2/3 of the patients had health problem accompanying COPD, they used oxygen therapy at home, they experienced severe-very severe dyspnea, and they used aftercare options to reduce complaints due to the disease (Table 1).

It was determined that caregivers participating in the study showed an equal distribution in terms of gender variable, and their average age was 63.28 ± 10.70 years. The majority of caregivers were married, had primary school education, and were housewives, and the average duration of care was 6.13 years. It was determined that caregivers were mostly children and spouses of the patients, most of them did not receive any information about providing care, almost all of them needed to get information about patient care, and the rate of those who considered themselves sufficient in the care they gave to the patient was low (Table 2).

When the care burden and quality of life scores of the caregivers before and after the training were compared, it was determined that care burden scores decreased, quality of life scores increased, and this difference between measurements was statistically significant in post-training follow-ups (Table 3).

At the end of the training, although the caregiver burden scores of female caregivers decreased, it was determined that the caregiver burden scores of the female caregivers were higher. It was observed that the caregiver burden was higher in caregivers <60 years of age. It was found that caregiver burden scores of caregivers who are high school graduates were lower than literate/primary school educated caregivers both in pre- and post-training period. While there was no significant difference in pre-training scores of caregiver burden in relevance with the occupational groups, caregiver burden scores of housewives were found to be significantly higher in post-training follow-up. It was determined that the number of people living at home and prior knowledge of caregiving did not make a significant difference in caregiver burden scores. It was also determined that the caregiver burden scores of the caregivers, those who had been caregivers for 6 years or more, those who had been providing care for their parents, and those who considered themselves "partially sufficient and inadequate" at caregiving were also significantly higher in post-training follow-ups.

When the caregivers' overall quality of life pre- and post-training scores were examined, the quality of life scores at the third month post-training follow-up of female, housewives, caregivers who had been giving care for 1-5 years, who had not received any information about caregiving, and who considered themselves self-sufficient in caregiving were significantly higher compared to the other groups' scores (Table 4).

DISCUSSION

Patients with COPD need the support of caregivers, especially in cases where functional losses progress and dependency levels increase. In many studies, it was reported that the majority of caregivers were female, they usually cared for their spouses,[9,14,21-23] and caregivers were mostly at a young age.[12,14,24] The fact that the majority of caregivers participating in the study were the children and spouses of the patients is similar to the previous study findings. However, the average ages of both caregivers (63 years and 79 years) were high in the study. It is a remarkable finding that caregivers who took the responsibility for taking care of elderly patients were also in the elderly group. This finding shows that the caregiver profile has started to change as a result of the prolonged life expectancy in societies and the gradual aging of societies. It can be suggested that as the age of the caregiver increases, age-related health problems and physical limitations may occur and the caregiving burden will increase. In some studies conducted with the caregivers of people who have chronic physical diseases, the caregiving burden was found to be higher in elderly caregivers, but age was reported not to be an important determinant of this burden.[25,26] However,

Table 1. Features of Patients

Feature	Number (%)
Gender	
Female	13 (40.6)
Male	19 (59.4)
Age 42-92 (79.88 ± 11.07) years	
Educational status	
Illiterate	4 (12.4)
Literate	19 (59.5)
Primary school	5 (15.6)
Middle school	1 (3.1)
High school	2 (6.3)
University	1 (3.1)
Marital status	
Married	15 (46.9)
Single	17 (53.1)
Family type	
Nuclear family	18 (56.3)
Extended family	8 (25.0)
Alone	6 (18.8)
Employment status	
Employed	0 (0.0)
Unemployed	32 (100.0)
Smoking status	
Smoker	1 (3.1)
Smoked but quit	17 (53.1)
Nonsmoker	14 (43.8)
Year of COPD diagnosis	
7 months-5 years	17 (53.1)
6 years-15 years	15 (46.9)
Hospitalization due to COPD in the recent years	
No hospitalization	7 (21.9)
Once	1 (3.1)
Twice	1 (3.1)
Three times and more	23 (71.9)
Application to the emergency room due to COPD in the past years	
Yes	21 (65.6)
No	11 (34.4)
Another health problem other than COPD	
Yes	21 (65.6)
No	11 (34.4)
Oxygen use at home	
User	20 (62.5)
Non-user	12 (37.5)
Aftercare	
User	13 (40.6)
Non-user	19 (59.4)
MRC dyspnea scale	
No dyspnea	1 (3.1)
Mild dyspnea	5 (15.6)
Moderate dyspnea	5 (15.6)
Severe dyspnea	5 (15.6)
Very severe dyspnea	16 (50.0)

COPD, chronic obstructive pulmonary disease; MRC Dyspnea Scale, Medical Research Council Dyspnea Scale.

Table 2. Features of Caregivers

Feature	Number (%)
Gender	
Female	16 (50.0)
Male	16 (50.0)
Age 46-80 (63.28 ± 10.70) years	
Marital status	
Married	28 (87.5)
Single	4 (12.5)
Educational status	
Literate	5 (15.6)
Primary school	17 (53.1)
High school	10 (31.3)
Occupation	
Housewife	16 (50.0)
Retired	11 (34.4)
Self-employed	5 (15.6)
Number of people living at home	
2	9 (28.1)
3	20 (62.5)
4-6	3 (9.4)
Duration of caregiving (year)	1-15 (6.13 ± 4.53)
The degree of relationship to the patient	
Parents	15 (46.9)
Spouse	15 (46.9)
Sibling	2 (6.3)
Prior knowledge about caregiving	
Yes	11 (34.4)
No	21 (65.6)
Self-sufficiency in caregiving	
Sufficient	10 (31.3)
Partially sufficient	18 (56.3)
Insufficient	4 (12.5)
Need for knowledge in caregiving	
Yes	31 (96.9)
No	1 (3.1)

the results obtained demonstrate that the number of elderly caregivers who provide care to elderly people will increase and health care systems should be prepared for this change in the caregiver profile.

It was determined that the caregivers who participated in the study have been working as a caregiver for an amount of time that cannot be said to be short (average 6 years). However, more than half of the caregivers reported that they needed to be informed about caregiving and that they did not find themselves competent in providing care. It has been shown that a longer period of caregiving is associated with higher care burden.[27] Therefore, it can be said that it is important to

Table 3. Mean Scores Caregivers Obtained from CBI and WHOQOL-Bref Quality of Life Scale in the Pre-training and Post-training Follow-Up Periods

	Before Training	Post-training First Month Follow-Up	Post-training Third Month Follow-Up		
Caregiver Burden Inventory	**(Mean ± SD)**	**(Mean ± SD)**	**(Mean ± SD)**	**F; *P***	**Difference**
Time-dependency burden	17.97 ± 2.376	16.81 ± 2.306	15.81 ± 2.191	137.406; .000***	1-2-3
Developmental burden	11.13 ± 3.087	8.00 ± 3.048	7.09 ± 2.821	185.932; .000***	1-2-3
Physical burden	14.96 ± 3.585	12.62 ± 3.762	11.29 ± 3.322	144.299; .000***	1-2-3
Social burden	8.88 ± 3.386	7.06 ± 3.151	6.09 ± 3.073	99.431; .000***	1-2-3
Emotional burden	6.09 ± 2.006	3.53 ± 1.218	3.28 ± 1.198	48.932; .000***	1-2.3
CBI total score	59.02 ± 9.12	48.02 ± 8.358	43.57 ± 8.08	427.893; .000**	1-2-3
WHOQOL-Bref Quality of Life Scale					
General status of health	8.69 ± 2.669	11.88 ± 1.431	12.75 ± 1.107	91.233; .000***	1-2-3
Physical domain	10.04 ± 1.399	11.96 ± 0.695	12.43 ± 0.681	80.354; .000***	1-2-3
Psychological domain	11.38 ± 0.957	12.00 ± 0.535	12.33 ± 0.718	11.250; .000***	1-2-3
Social domain	10.42 ± 1.987	11.83 ± 0.738	12.42 ± 0.924	20.384; .000***	1-2-3
Environmental domain	11.73 ± 1.862	12.47 ± 1.513	12.66 ± 1.450	28.881; .000***	1-2-3
Total score	52.25 ± 5.322	60.14 ± 2.315	62.58 ± 2.271	105.244; .000***	1-2-3

***$P < .001$; 1 = first follow-up; 2 = second follow-up; 3 = third follow-up.
SD, Standard Deviation; F, Repeated Measurements Analysis of Variance (Repeated Measurements); Difference, Bonferroni test; P, significance level.

provide professional support and counseling by nurses to the caregivers of patients with COPD.

It was determined that the care burden of the caregivers who took care of elderly and dependent patients was high and their quality of life decreased.[14] It is stated that caregivers of patients with COPD experience many physical and psychosocial difficulties, exhaustion, and difficulties in providing care; their quality of life is negatively affected.[9,28,29] Wang et al[30] reported that in order to improve self-care behaviors among COPD patients, both patients and their caregivers should be provided with training on COPD to increase their level of knowledge of the disease.

In the study, it was determined that in the pre-training period, caregiver burden was high, quality of life was low, and in the post-training period, there was a significant decrease in care burden and a significant increase in quality of life in follow-ups ($P < .001$). This result shows that the training organized in accordance with the learning needs of the caregivers of patients with COPD contributed to the conscious fulfillment of the caregivers' responsibilities, to the decrease in the care difficulties and care burdens, and to the increase in their quality of life. Professional support which will be provided to caregivers in supporting the care needs and comfort living of caregivers and patients, especially in healthcare systems where home care services are not becoming widespread, will be the most important intervention.

Nakken et al.[27] in their study with spouses of COPD patients, determined that women sought less social support, more symptoms of passive reaction and anxiety were observed in them, and their health was worse. In the study, it was concluded that in the post-training, the care burden of female caregivers and caregivers who were housewives was higher and both of their quality of life scores were lower. When these 2 findings are evaluated together, it can be said that female caregivers have taken caregiver responsibilities in addition to their responsibilities as housewives, spouses, and children and that this had an impact on these findings.

Salama and El-Soud[32] reported that caregiver burden increased when the education level of the caregiver decreased, and Bicki[33] stated that education led to a decrease in the average scores of care burden. In this study, caregivers had lower levels of caregiver burden and higher quality of life scores due to their high school and higher education level, and this made us think that they used the information and training channels more efficiently in order to do a better job in caregiving and therefore they experienced less caregiver burden.

It was determined that caregivers who lived with COPD patients experienced serious physical and emotional problems.[14] It was reported that the caregiver burden causes conditions such as depression, anxiety, burnout, decrease in physical health, social isolation, and economic difficulties.[34] Around 63.5% of family caregivers were found to have symptoms of anxiety.[35] It has been emphasized that anxiety and depression levels of caregivers are inversely related to having provided care for a patient before, duration of care, social support, and leisure activities.[29] It was stated in some intervention studies that interventions made to caregivers made positive contributions against anxiety.[36,37]

It was determined that caregivers who cared for the patient who did not have severe COPD and who could get help from others had lower anxiety levels.[38] In some studies, it was

Table 4. Average of Caregiver Burden and Quality of Life Scores According to Some Descriptive Characteristics of Caregivers

		Caregiver Burden Inventory Total Score			Total Score of the WHOQOL-Bref Quality of Life Scale		
		Before the Training Mean ± SD	After the Training First Month Follow-up Mean ± SD	After the Training Third Month Follow-up Mean ± SD	Before the Training Mean ± SD	After the Training 1st Month Follow-up Mean ± SD	After the training 3rd Month Follow-up Mean ± SD
Gender	Female	62.06 ± 11.745	51.91 ± 10.45	47.78 ± 9.758	50.52 ± 5.807	60.06 ± 2.170	63.69 ± 1.590
	Male	55.98 ± 3.786	44.14 ± 1.681	39.36 ± 1.381	53.98 ± 4.297	60.23 ± 2.520	61.48 ± 2.349
	t; *P*	1.970; .058	2.933; .006**	3.418; .002**	−1.913; .065	−0.208; .837	3.122; .004**
Age	45-60 years old	61.37 ± 9.617	50.99 ± 9.536	45.66 ± 9.553	51.08 ± 4.768	60.80 ± 1.815	62.75 ± 2.704
	61-80 years old	56.37 ± 8.022	44.67 ± 5.293	41.20 ± 5.382	53.57 ± 5.764	59.40 ± 2.643	62.40 ± 1.732
	t; *P*	1.585; .124	2.273; .030*	1.597; .121	−1.335; .192	1.766; .088	0.427; .673
Educational status	Literate/primary school	61.42 ± 9.512	50.31 ± 8.725	46.13 ± 7.971	51.58 ± 5.940	59.91 ± 2.257	62.90 ± 1.454
	High school	53.75 ± 5.530	43.00 ± 4.708	37.95 ± 5.063	53.72 ± 3.429	60.64 ± 2.484	61.90 ± 3.475
	t; *P*	2.362; .025*	2.475; .019*	2.968; .006**	−1.053; .301	−0.818; .420	1.160; .255
Occupation	Housewife	62.06 ± 11.745	51.91 ± 10.458	47.78 ± 9.758	50.52 ± 5.807	60.06 ± 2.170	63.69 ± 1.590
	Retired/self-employed	55.98 ± 3.786	44.14 ± 1.681	39.36 ± 1.381	53.98 ± 4.297	60.23 ± 2.520	61.48 ± 2.349
	t; *P*	1.970; .058	2.933; .006*	3.418; .002*	−1.913; .065	−0.208; .837	3.122; .004*
Number of people living at home	2 people	60.36 ± 8.165	49.58 ± 7.404	44.36 ± 7.171	50.90 ± 3.721	58.90 ± 1.964	63.38 ± 1.665
	3 people and above	58.50 ± 9.592	47.41 ± 8.781	43.26 ± 8.542	52.78 ± 5.818	60.63 ± 2.295	62.27 ± 2.429
	t; *P*	0.513; .612	0.654; .518	0.341; .735	−0.891; .380	−1.991; .056	1.256; .219
Duration of caregiving	1-5 years	54.77 ± 7.151	45.03 ± 6.533	40.56 ± 5.416	55.45 ± 4.064	60.75 ± 2.699	63.59 ± 2.387
	6 years and above	63.28 ± 9.065	51.02 ± 9.087	46.58 ± 9.291	49.05 ± 4.496	59.54 ± 1.734	61.58 ± 1.673
	t; *P*	−2.950; .006**	−2.139; .041*	−2.237; 0.033*	4.220; .000***	1.510; .141	2.765; .010*
The degree of relationship of the patient to the caregiver	Parents	63.07 ± 8.774	52.18 ± 9.302	46.78 ± 9.613	50.17 ± 4.217	60.43 ± 0.738	62.12 ± 2.08
	Spouse/sibling	55.46 ± 8.065	44.35 ± 5.392	40.74 ± 5.239	54.08 ± 5.630	59.89 ± 3.124	63.00 ± 2.414
	t; *P*	2.557; .016*	2.957; .006**	2.246; .032*	−2.199; .036*	0.657; .516	−1.093; .283
Information obtaining status	Yes	59.55 ± 4.362	46.25 ± 3.453	41.43 ± 4.128	50.07 ± 2.562	58.73 ± 1.487	60.79 ± 1.331
	No	58.75 ± 10.92	48.95 ± 9.983	44.69 ± 9.427	53.39 ± 6.053	60.88 ± 2.354	63.52 ± 2.103
	t; *P*	0.231; .819	−0.865; .394	−1.087; .286	−1.730; .094	−2.738; .010*	−3.896; .001**
Self-sufficiency in caregiving	Sufficient	64.93 ± 11.175	56.18 ± 9.092	51.78 ± 8.191	50.96 ± 6.721	61.44 ± 1.107	63.89 ± 1.089
	Partially sufficient/insufficient	56.34 ± 6.724	44.32 ± 4.654	39.84 ± 4.585	52.84 ± 4.615	59.55 ± 2.494	61.99 ± 2.435
	t; *P*	2.707; .011*	4.918; .000*	5.301; .000**	−0.922; .364	2.280; .030*	2.341; .026*

*p < 0.05; **p < 0.01; ***p < 0.001.
SD, Standard Deviation; t, Independent Sample T-Test; *P*, Significance Level.

shown that the duration of care was a variable[39] that affected the care burden, and the care burden of caregivers increased as the care duration increased.[40] In the study, most of the caregivers stated that their physical health was affected due to caregiving, and it was determined that caregivers had a high care burden. This result is thought to have evolved as a result of the majority of caregivers have had to care for their elderly parents for years.

Cedano et al.[41] in their study with caregivers of patients with COPD, determined that all dimensions of quality of life were affected by care burden. In the study, it was found that caregivers had low quality of life scores, and there was a significant post-training increase in quality of life scores. This result shows that the training provided in content that meets the learning needs of caregivers is effective in improving the quality of life of caregivers.

CONCLUSION

COPD patients who participated in the study were mostly taken care of by their spouses and children. The majority of patients with COPD and their caregivers consisted of older individuals. It was observed that the care burden of the caregivers, where the gender of men and women were distributed equally, was high and the quality of life was low. It was determined that the training created based on defining the learning needs of caregivers was effective in decreasing the care burden of caregivers and increasing the quality of life. Training and counseling services to be provided by nurses to caregivers will reduce the care difficulties of both caregivers and patients and support their quality of life.

Limitations

In this study, which has a relatively small sample size, the care burden and quality of life perceived by the caregivers of patients with COPD were discussed. In this study, the evaluation of caregivers' perceptions of care was identified on the basis of socio-demographic characteristics. In studies to be conducted with larger samples, by making in-depth evaluation of the health status of caregivers, the relationship between perceived care burden and health problems may be examined. Studies examining the effects of the training given to caregivers of patients with COPD on their caregiving quality may be carried out.

Ethics Committee Approval: This study was approved by Ethics committee of Sivas Cumhuriyet University, (Decision No: 2018-12/06, Date:05.12.2018).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors have no conflict of interest to declare.

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Original Article

Is the Thoracic and Back Muscle Mass Associated with Disease Severity in Patients with COVID-19?

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Abstract

OBJECTIVE: With this study, it was aimed to investigate whether the thoracic muscle mass of patients with coronavirus disease 2019 was related to disease severity and disease characteristics and to evaluate whether muscle mass measurement had a predictive effect on predicting disease severity.

MATERIAL AND METHODS: Two hundred twenty-three subjects (patient group = 161 and control = 62) who presented to our coronavirus disease 2019 outpatient clinic between May 2020 and September 2020 were included in the study. The medication, oxygen, and intubation requirements of the patients and their disease duration and hospital stay were also recorded. At the T4 level, thoracic and back (pectoralis, intercostalis, paraspinals, serratus, and latissimus dorsi) muscles and at the T12 level erector spinae muscles were measured in terms of area (cm^2).

RESULTS: T4-level muscle cross-sectional area results were found to be negatively correlated with the presence of pneumonia and the requirement of oxygen and intubation. In addition, both T4- and T12-level muscle cross-sectional area results were factors associated with oxygen and intubation requirements. T4-level muscle cross-sectional area results were also associated with the presence of pneumonia.

CONCLUSION: We predict that there may be a relationship between the decrease in the mass of the accessory respiratory muscles and the severity of the disease.

KEYWORDS: COVID-19, disease severity, erector spinae muscles, thoracic muscle mass
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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus, which continues to spread increasingly all over the world.[1] This virus emerged in China last year is new for the whole world. Coronavirus disease 2019 can cause a wide range of clinical pictures from a mild flu infection to pneumonia, pulmonary edema, multi-organ failure, and death.[2]

Studies to understand the disease and to prevent the progression as well as to develop treatment and diagnostic methods for COVID-19 continue all over the world. Despite these prevention methods, the contagiousness of the SARS-CoV-2 virus is high and there are currently over 36 million patients in the world. Although most of the symptomatic infections are mild, patients with initially mild symptoms can quickly cause a marked alveolar inflammatory cell infiltration that progresses to acute respiratory distress syndrome and eventually to multi-organ failure.[3]

Therefore, disease-related factors and progression should be investigated and preventive methods should be developed to alleviate infections and prevent progression.

Although we learn new things about COVID-19 every day, studies defining risk factors and risk groups are still insufficient and incomplete.[4-7] There is no study investigating the relationship between the disease and the thoracic region, including the pulmonary system, which causes high mortality. Considering that respiratory function occurs with the contraction and expansion of the muscles in the thoracic cavity, it can be predicted that the muscle mass in this region will be effective in the progression of the disease. However, this information is still not based on scientific evidence.

Therefore, in this study, it was aimed to investigate whether the thoracic and back muscle mass of patients with COVID-19 was related to disease severity and disease characteristics and to evaluate whether muscle mass measurement had a predictive effect on disease severity.

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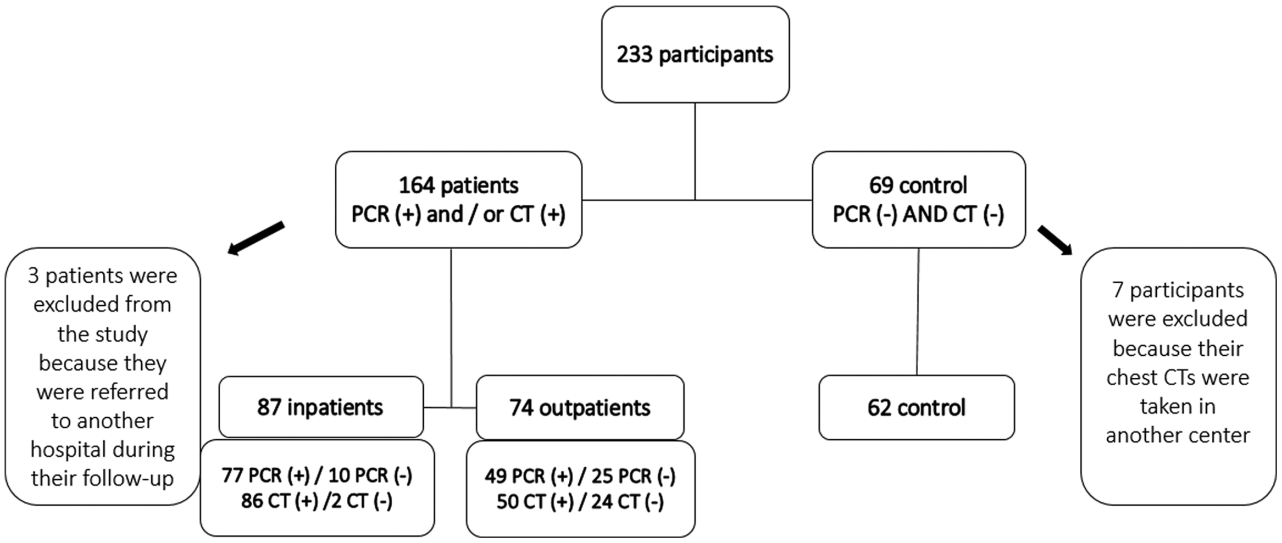


Figure 1. Selection of participants.

Our hypothesis in this study was that low thoracic muscle mass might increase the severity of the COVID-19 clinical picture.

MATERIAL AND METHODS

Study Design and Selection of Participants

Two hundred thirty-three participants who presented to our COVID-19 inpatient and outpatient clinics between May 2020 and September 2020 were included in the study.

Of these participants, who were followed up and treated according to the national COVID-19 diagnosis and treatment algorithm, 164 patients with positive antigen test [polymerase chain reaction (PCR)] or positive computed tomography (CT) findings or presence of both parameters positive were evaluated as the patient group, and 69 patients with negative test and negative CT findings were evaluated as the control group. Three patients from the patient group were excluded from the study because they were referred to another hospital during their follow-up and 7 participants from the control group were excluded because their chest CTs were taken in another center. The study was completed with 223 participants (patient group n = 161, control group n = 62) (Figure 1).

Inclusion criteria for the study were as follows: patients aged 18-75 years who underwent PCR and CT evaluations within the first 10 days after the onset of symptoms and who were followed up in the COVID-19 outpatient clinic of our pandemic hospital were included in the study.

MAIN POINTS

- Polymerase chain reaction positivity and the presence of pneumonia on computed tomography are associated with age, body mass index, and comorbidities.
- Muscle cross-sectional areas at both T4 and T12 levels correlate with oxygen and intubation requirements.
- There may be a relationship between the decrease in the mass of the auxiliary respiratory muscles and the severity of the disease.

Patients older than 75 years (to eliminate the possibility of age-related sarcopenia), with a history of surgery and trauma in the thoracic region, with known progressive/non-progressive neurologic disease, with a history of advanced lung disease or malignancy, and those with inflammatory lung diseases were not included in the study.

Before evaluations, the patients were given verbal and written information on the nature of the study. Informed consent forms were signed upon admission to the trial. All procedures were conducted in accordance with the relevant principles of the Helsinki Declaration. Also, approval of the study was obtained from the University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital Ethics Committee (Number: 91/09, Date: July 06, 2020).

The demographic characteristics of all participants including age, sex, job, body mass index (BMI), presence of additional comorbidity, smoking status, and smoking pack/years were recorded. In addition, the medication, oxygen, and intubation requirements of the patients and duration of disease and hospital stay were also recorded. Outpatient participants were followed up for 14 days until the PCR became negative or until the 14-day treatment was completed according to the national COVID-19 diagnosis and treatment algorithm; the control group was followed up for 14 days.

Positivity in PCR and CT was evaluated as disease characteristics. Coronavirus disease 2019 lung involvement was evaluated as suggested by the partnership of Radiological Society of North America, Society of Thoracic Radiology, and American College of Radiology, and it was recorded as having pneumonia or normal.[8-10]

Non-contrast chest CT was performed using a 16-detector CT scanner (Somatom Emotion 16; Siemens Healthcare, Erlangen, Germany) in the radiology department of our hospital. T4 and T12 levels were defined as reported in previous studies.[11] The close polygon region of interest tool (NIH-Image J software program) was used to trace the contour of the muscle of interest on T4- and T12-level images for cross-sectional area (CSA) measurements. At the T4 level, thoracic

and back (pectoralis, intercostalis, paraspinals, serratus, latissimus dorsi) muscles and at the T12 level erector spinae muscles were measured in terms of area (cm^2) (Figure 2).

Study Protocol

The measurements of the CT images were made separately by 2 blind specialists. Each expert took 3 measurements and the 3 measurements were averaged. Then, a single result was generated from the arithmetic mean of the 2 experts' measurements. To prevent bias, the group allocation of the participants was not shared with the specialists.

All participants were divided into 2 groups, the patient group and the control group, and the parameters were compared between the 2 groups. Later, the patient group was separated as outpatients and inpatients, and the parameters were compared between these groups. Muscle mass results were compared with all parameters to evaluate the factors that might be associated with muscle mass and disease severity.

Statistical Analysis

All statistical analyses were carried out by using Statistical Package for the Social Sciences (version 15.0) for Windows statistical package. The variables were investigated using an analytical method (Kolmogorov-Smirnov test) to assess whether or not they are normally distributed. Descriptive statistics were demonstrated as median (minimum-maximum) for continuous variables and as a percentage (%) for nominal variables. The difference between 2 groups' comparison was evaluated using the Mann–Whitney *U* test. In order to evaluate the relation between T4-T12 levels and evaluation parameters, Spearman's rho correlation test was performed for continuous variables and univariate analysis for nominal variables. For statistically significant correlations, the age, gender, and comorbidity presence-adjusted model multivariate regression analysis using control group as dependent variable was performed. A *P* value of .05 or less was considered significant.

RESULTS

Two hundred twenty-three participants (161 (72.2%) patients and 62 (27.8%) controls) were included in the study. The median age of all participants was 46.00 (range, 19.0-75.0) years; 120 (53.8%) were women 103 (46.2%) were men. The distribution of the disease characteristics including the demographic and muscle CSAs at the T4 and T12 levels of the patient and control groups is presented in Table 1.

Among the patient and control groups, age (P = .001), BMI (P = .001), and T4- and T12-level muscle CSAs (both for P = .001) were lower in the patient group, and the number of additional comorbidities was higher in this group (P = .004).

Seventy-four (46%) of the patients were treated as outpatients, and 87 (54%) were treated in the hospital. Inpatients and outpatients were compared in terms of demographic and disease characteristics (Table 2). The median number of days of oxygen need of inpatients was 5.0 (range, 1.0-32.0), the median intubation time was 0.0 (range, 1.0-12.0) days, and the median length of hospital stay was 8.0 (range, 1.0-32.0) days. The age (P = .001), presence of additional comorbidities (P = .022), the number of patients with PCR (P = .003), CT (P = .004) positivity, medication use (P = .022), oxygen (P = .001), and intubation (P = .001) in inpatients was significantly higher. T4- and T12-level muscle CSAs were lower in inpatients (P = .003, P = .004, respectively).

T4- and T12-level CSAs of the patients were negatively correlated with age (Spearman's rho correlation coefficient (r) = −0.161, P = .042 and r = −0.104, P = .045, respectively). No relationship was found with BMI (r = 0.026, P = .743 and r = 0.061, P = .446, respectively). The univariate regression analysis results of the patients' T4- and T12-level muscle CSAs, demographic, and disease characteristics are presented in Table 3.

T4-level muscle CSAs were found to be negatively correlated with the presence of pneumonia and the requirement of oxygen and intubation.

For significant correlations, as a result of age-, sex- and comorbidity-adjusted multivariate regression analysis, both T4- and T12-level muscle CSAs were factors associated with oxygen and intubation requirement. In addition, T4-level

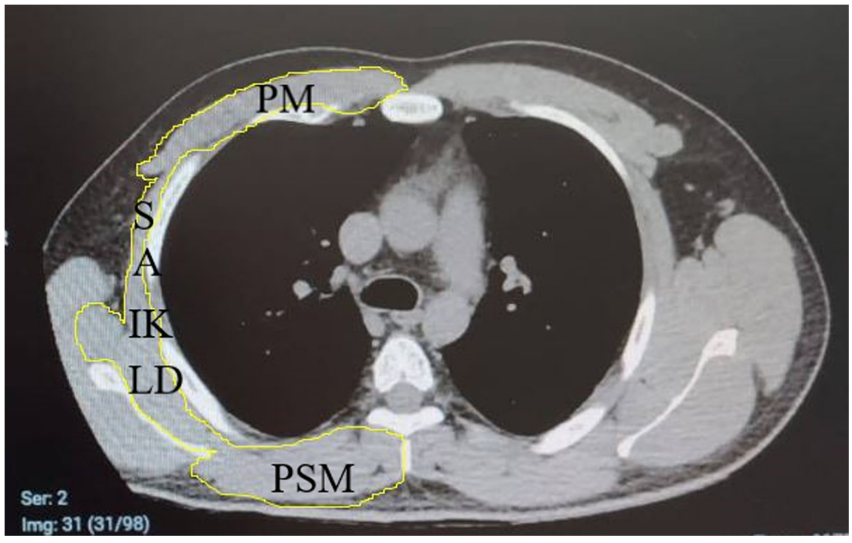


Figure 2. T4 level axial computed tomography image.

Table 1. Distribution and Comparison of Demographic and Disease Characteristics of Patient and Control Groups

	Patients (n = 161)	Controls (n = 62)	*P*
Age, med (min-max)	53.0 (19.0-75.0)	34.0 (19.0-68.0)	**.001***
Sex, n (%)			
Female	91 (56.5)	29 (46.8)	.196
Male	70 (43.5)	33 (53.2)	
BMI (%), med (min-max)	27.79 (17.83-43.34)	25.44 (18.42-37.20)	**.001***
Job, n (%)			
White collar	30 (18.6)	22 (35.5)	.884
Blue collar	46 (28.6)	23 (37.1)	
Non-working	85 (52.8)	17 (27.4)	
Additional comorbidity, n (%)	79 (49.1)	16 (25.8)	
Diabetes mellitus	3 (1.9)	1 (1.6)	**.004***
Hypertension	61 (37.9)	6 (9.7)	
Coronary artery disease	10 (6.2)	3 (4.8)	
Hypothyroidism	3 (1.9)	3 (4.8)	
Osteoarthritis	2 (1.2)	3 (4.8)	
Smoking, n (%)			
Active smoking	23 (14.3)	21 (33.9)	.106
Not smoking	125 (77.6)	34 (54.8)	
Stopped smoking	13 (8.1)	7 (11.3)	
Smoking (pack/years), med (min-max)	0.0 (0.0-50.0)	3.0 (1.0-4.0)	.338
PCR positivity, n (%)	126 (78.3)	0	**.001***
Pneumonia (CT) positivity, n (%)	136 (84.5)	0	**.001***
T4-level muscle CSA (cm^2), median (min-max)	38.39 (10.14-92.34)	53.17 (21.65-198.70)	**.001***
T12-level muscle CSA (cm^2), med (min-max)	19.49 (14.05-77.28)	32.79 (15.94-79.60)	**.001***

BMI, body mass index; PCR, polymerase chain reaction; CT, computed tomography; CSA, cross-sectional area; med, median; min, minimum; max, maximum.
*$P < .05$.

muscle CSAs were also associated with the presence of pneumonia (Table 4).

DISCUSSION

In this study, it was aimed to investigate the relationship between T4- and T12-level muscle mass CSAs in patients with COVID-19 and the demographic and disease characteristics of the patients. As a result of the study, it was found that patients who were PCR positive and with the presence of pneumonia on CT were older, had higher BMI, and had more comorbidities compared with the control group. Also, it was found that patients with advanced age and comorbidities had the presence of pneumonia on CT and needed hospitalization. T4- and T12-level muscle CSAs were found lower in the patient group than in the control group, as well as lower in inpatients compared to outpatients. It was found that these levels of muscle CSAs were associated with the need for oxygen and intubation and that the T4-level CSA was also associated with the presence of pneumonia.

The SARS-CoV-2 virus appears as a simple respiratory tract infection at levels ranging from mild disease to sepsis. In its clinical classification, the World Health Organization divides COVID-19 as mild symptomatic disease, pneumonia, severe pneumonia, acute respiratory distress syndrome, sepsis, and advanced stage with septic shock.[12] According to the September 2020 data of the European Centers for Disease Prevention and Control, it was reported that most patients with COVID-19 had an asymptomatic or mild course of the disease, 21-25% needed hospitalization, and 9% required intensive care treatment.[13] In our study, the rate of inpatients was 39% when all symptomatic patients (regardless of PCR and CT results) were considered. This situation is probably related to our health system because this study was conducted in a pandemic hospital. In other words, it is a place where patients are sent to an upper center from clinics that provide primary health care. This is not the first place where most patients are admitted. Therefore, patients with more pronounced symptoms and thought to be progressive may have applied to us or been referred to a primary health care center.

The need for hospitalization and intensive care increases both morbidity and mortality in individuals and socioeconomic burden in countries. Studies for this purpose have been conducted to determine in which patient the condition will be

Table 2. Demographic and Disease Characteristics of Patient Groups

	Inpatient (n = 87)	Outpatient (n = 74)	*P*
Age, med (min-max)	58.0 (19.0-75.0)	44.50 (19.0-75.0)	**.001***
Sex, n (%)			
Female	45 (51.7)	46 (62.2)	.184
Male	42 (48.3)	28 (37.8)	
BMI (%), med (min-max)	29.04 (17.83-41.79)	26.54 (20.62-43.34)	.068
Additional comorbidity, n (%)	60 (69.0)	33 (44.6)	**.022***
Smoking, n (%)			
Active smoking	9 (10.3)	14 (18.9)	.206
Not smoking	8 (9.2)	55 (74.3)	
Stopped smoking	70 (80.5)	5 (6.8)	
Smoking (pack/years), med (min-max)	0.0 (0.0-50.0)	0.0 (0.0-35.0)	.743
PCR positivity, n (%)	77 (88.5)	49 (66.2)	**.004***
Pneumonia (CT) positivity, n (%)	86 (98.9)	50 (67.6)	**.003***
Medication, n (%)			
HCQ	87 (100)	48 (64.9)	**.022***
Anticoagulant	72 (82.8)	5 (6.8)	
AZT	71 (81.6)	19 (25.7)	
FVP	38 (43.7)	34 (45.9)	
Paracetamol	49 (56.3)	2 (2.7)	
Steroid	17 (19.5)	0	
Other (plasma therapy, other antiviral, etc.)	49 (56.3)	1 (1.4)	
Number of patients in need of oxygen, n (%)	87 (100)	0	**.001***
Number of intubated patients, n (%)	5 (5.7)	0	**.001***
T4-level muscle CSA (cm^2), med (min-max)	37.07 (10.14-86.90)	39.43 (19.81-92.34)	**.003***
T12 level muscle CSA (cm^2), med (min-max)	19.17 (14.05-31.11)	21.57 (14.86-67.28)	**.005***

BMI, body mass index; PCR, polymerase chain reaction; CT, computerized tomography; CSA, cross-sectional area; med, median; min, minimum; max, maximum; HCQ, hydroxychloroquine; AZT, azithromycin; FVP, favipiravir.
*$P < .05$.

aggravated and risk factors for the severe course of the disease. These studies were found that disease and demographic characteristics such as advanced age, presence of additional comorbidities, and smoking have been defined as risk factors for severe disease.[4-7] In our study, age was significantly higher and additional comorbidities were higher in the patient group compared with the controls as well as in inpatients compared with outpatients. These results confirm that COVID-19 pneumonia will be more prevalent in patients with advanced age and additional comorbidities because all of our inpatients had severe pneumonia requiring oxygen support and these patients were older and had more comorbidities.

The interesting point of the study was that more than half of the outpatients who were followed up had lung involvement findings of COVID-19 (67.6%). Although the outpatient's median age value was lower than the inpatient group, there was no significant difference between patient groups. In other words, although outpatients had lung involvement, they were not at a level that required oxygen support. In previous studies, it has been reported that some individuals with very severe COVID-19 disease have severe lung damage and decrease in diffusion capacity with lung fibrosis.[14] It has been shown that some of these patients can recover completely, whereas others experience serious morbidity or even mortality. We think that the reason for this is related to low muscle mass in the thoracic region, which we demonstrated in our study. The respiratory system consists of the lung which provides the exchange of respiratory gases and the chest wall and respiratory muscles which pump out exhaled gases (expiration).[15] Moreover, lung ventilation is a mechanical process in which the respiratory muscles act together to allow air in and out of the lungs. Any change in the performance of the respiratory muscles can reduce the effectiveness of ventilation.[15] The inspiratory muscles that help the thoracic cavity to expand are the diaphragm, intercostal, and parasternal muscles (e.g., pectoralis, serratus, and latissimus), and the expiratory muscles that provide compression of the thoracic cavity are the abdominal muscles and paraspinal muscles. In respiratory function, the primary inspiratory muscle is the diaphragm, and the expiratory muscles are the abdominal muscles. Other muscles, namely accessory muscles come into play when dysfunction in the respiratory system occurs and in the increase of metabolic need such as exercise.[16] Studies

Table 3. Univariate Analysis of T4- and T12-Level Muscle CSAs and Demographic and Disease Characteristics of Patients

	β	SE	*P*	95% CI (LL/UL)
T4-level CSA				
Sex	0.605	0.793	.447	0.068/0.959
Additional comorbidity	−2.400	0.827	.059	−4.039/−0.762
Active smoking	−2.388	2.365	.316	−0.792/−1.316
PCR positivity	4.062	2.970	.173	−1.791/9.915
Pneumonia presence	−15.08	2.70	**.001***	−20.422/−9.749
Need of oxygen	−16.095	2.929	**.001***	−22.767/−11.222
Need of intubation	−17.859	6.949	**.012***	−31.683/−4.035
T12-level CSA				
Sex	−1.879	0.914	.071	−3.681/−0.077
Additional comorbidity	0.211	0.146	.150	−0.078/0.501
Active smoking	−0.519	0.490	.214	−1.491/0.453
PCR positivity	−2.623	0.830	.068	−4.259/−0.986
Pneumonia presence	−3.387	0.265	**.001***	−5.193/−1.580
Need of oxygen	−4.313	0.892	**.001***	−6.072/−2.555
Need of intubation	−3.913	1.382	**.006***	−6.660/−1.166

SE, standard error; LL, lower level; UL, upper level; PCR, polymerase chain reaction; CSA, cross-sectional area.
*$P < .05$.

conducted on patients in intensive care with COVID-19 disease have shown that an extreme hypermetabolic process occurs and that this may be a major contributing factor to the extraordinary ventilatory and oxygenation demands in patients with COVID-19.[17,18] Based on this hypothesis, we measured the CSA of accessory respiratory muscles at the T4 and T12 levels.

As a result of the study, we found that there was a significant decrease in muscle mass in the patient group compared with the control group as well as in inpatients compared with outpatients. Moreover, we found that the muscle mass CSAs at the T4 and T12 levels were associated with oxygen and intubation requirements as independent of age, sex, and the presence of comorbidities. There is little information in the literature evaluating the relationship between disease severity and thoracic muscle mass in patients with COVID-19. In fact, as far as we know, this study is the first to examine both thoracic and back muscles mass in patients with COVID-19. Some studies in the literature were performed in patients with chronic obstructive pulmonary disease and pulmonary fibrosis, including measurements of the same levels and muscles similar to our study. These studies have shown that muscle CSAs were associated with symptoms, severe airflow limitation, emphysema severity, prognosis, and mortality.[19-22] We think that these results show that people with high muscle mass CSAs can compensate the respiratory problems caused by COVID-19 without the need for oxygen or even hospitalization and those with low muscle mass CSAs can fall into a decompensation that may need external support.

The most important limitation of our study is that we could not include healthy individuals without symptoms. The participants we received as a control group were individuals who showed symptoms of COVID-19 but were not diagnosed as having COVID-19 according to the international

Table 4. Multivariate Regression Analysis for Significantly Correlations

	β	SE	*P*	95% CI (LL/UL)
T4-level CSA				
Pneumonia presence	−16.232	3.471	**.006***	−23.073/−9.391
Need of oxygen	−10.718	4.613	**.021***	−19.810/−1.627
Need of intubation	−16.714	6.554	**.013***	−29.749/−3.678
T12-level CSA				
Pneumonia presence	−2.996	0.925	.309	−8.813/−2.281
Need of oxygen	−7.509	2.926	**.014***	−13.226/−2.667
Need of intubation	−4.040	1.340	**.003***	−6.704/−1.376

SE, standard error; LL, lower level; UL, upper level; CSA, cross-sectional area.
*$P < .05$.

COVID-19 criteria. To avoid an unnecessary radiation load, we could not recruit healthy individuals for the study. In addition, we could not include the diaphragm and abdominal muscles, which play a primary role in respiratory function. We think that large-scale studies that include these muscles will make our results more understandable.

CONCLUSION

We still know very little about COVID-19. In this study, it has been shown that decreased mass of the muscles defined as accessory respiratory muscles at the T4 and T12 levels is associated with the need for oxygen and intubation. We think that if the mass of these accessory muscles decreases, it can be predicted that the disease will progress seriously and that the respiratory load cannot be compensated.

Ethics Committee Approval: This study was approved by Ethics committee of University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital (Aproval No: 91/09).

Informed Consent: Informed consent forms were signed upon admission to the trial.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Z.AY., E.KU., G.A., M.ÇE.; Design – Z.AY., E.KU., G.A., M.ÇE.; Supervision – Z.AY., E.KU.; Resources – Z.AY., E.KU., G.A., M.ÇE.; Materials – Z.AY., E.KU., G.A., M.ÇE.; Data Collection and/or Processing – Z.AY., E.KU., G.A., M.ÇE.; Analysis and/or Interpretation – Z.AY., E.KU., G.A., M.ÇE.; Literature Search – Z.AY., E.KU., G.A., M.ÇE.; Writing Manuscript – Z.AY., E.KU., G.A., M.ÇE.; Critical Review – Z.AY., E.KU., G.A., M.ÇE.

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Original Article

Can Thorax Computed Tomography Severity Score in Coronavirus Disease 2019 Patients Differentiate Smokers from Non-smokers?

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Abstract

OBJECTIVE: The aim of this study was to explore the impact of smoking history on the severity of coronavirus disease 2019 radiologic findings. Therefore, we compared the computed tomography severity scores of smoking coronavirus disease 2019 patients with those of non-smoking coronavirus disease 2019 patients.

MATERIAL AND METHODS: A total of 121 patients were included in our study group. We retrospectively reviewed 121 patients who underwent reverse transcription-polymerase chain reaction sampling and computed tomography examination in our hospital between April 1, 2020, and July 30, 2020. All computed tomography images were independently reviewed by 2 radiologists.

RESULTS: There were 15 (12.4%) active smokers, 38 (31.4%) former smokers, and 68 (56.2%) never-smokers in this study. Among the 85 patients with evidence of pneumonia in thorax computed tomography, mean computed tomography severity scores were 8.02 and standard deviation 5.812. Computed tomography severity scores for patients with pathological computed tomography scans (n = 85) were performed for evaluating smoking status (never-smokers and smokers). We found a statistically significant relationship between computed tomography severity scores of never-smokers (n = 39) and smokers (n = 46) ($Z = 2.243$, $P = .025$). The computed tomography severity scores threshold for differentiating smokers in our study group was 8, with a sensitivity of 52.2% and a specificity of 79.5%. Among the 121 patients, 34 (28.1%) were in the asymptomatic group, 36 (29.75%) were in the mild group, 28 (23.14%) were in the common group, and 23 (19.0%) were in the severe group with severe pneumonia and respiratory distress. Five (1.47%), 16 (44.44%), 14 (50%), and 18 (78.26%) of the patients in these groups were smoking, respectively.

CONCLUSION: Among coronavirus disease 2019 patients, smoking is associated with the progression of the disease and increased adverse effects. In our study, smoking status was significantly correlated with thorax computed tomography findings on admission. Computed tomography severity scores assessment helps to evaluate the disease extent in coronavirus disease 2019 patients.

KEYWORDS: Computed tomography, COVID-19, CT severity score, smoker, smoking
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INTRODUCTION

A new epidemic of unknown disease occurred in Wuhan City, China, at the end of December 2019.[1] The novel coronavirus was established as the source of deep sequencing analysis of samples of the respiratory tract on January 7, 2020. The novel coronavirus is now called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1,2]

Severe acute respiratory syndrome coronavirus-2 is a part of the coronavirus family, whose name derives from the crown-like appearance of the virion. This feature is due to a glycosylated cell surface spike (S) protein containing 2 main domains, S1 and S2. The SARS-CoV-2 host cell input site is angiotensin-converting enzyme-2 (ACE2). The viral spiked envelope's S2 domain has a high affinity to the ACE2 receptor, which is present in several human organs, particularly the lung epithelium.[3,4] The expression of ACE2 among smokers has been high.[4] Smokers also experience increased ACE2 gene expression in type-2 pneumocytes and alveolar macrophages, especially at the terminal portion of the small airway epithelium, a finding that is not observed in those who never smoked. Smoking increases the risk of coronavirus disease 2019 (COVID-19) and the severity of the disease by causing lung damage.[4,5]

Smoking is linked to progression to serious illness, as substantial research has shown the detrimental effect of smoking habits on lung health and its causal connection with a variety of respiratory diseases.[6] Smoking affects the junctions between cells, leading to increased epithelial permeability, and reduces resistance to infections by impairing mucociliary clearance, causing peribronchiolar inflammation and damaging the immune system.[7,8] Previous studies report that smokers are twice as likely to catch the flu as non-smokers and experience more severe effects. Smokers had higher mortality rates in the previous epidemic of Middle East respiratory syndrome.[9,10] Middle East respiratory syndrome coronavirus belongs

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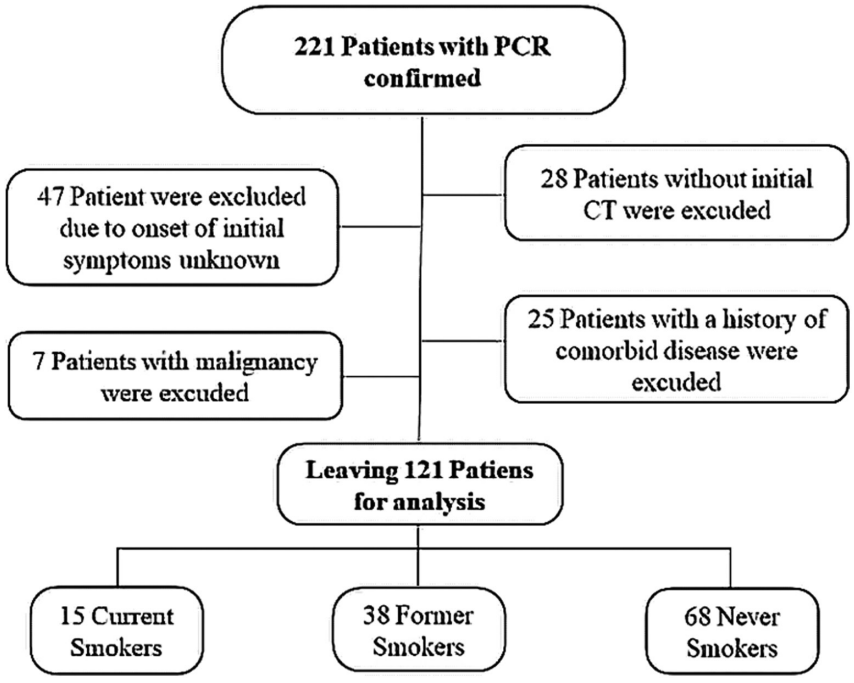


Figure 1. Recruitment flow chart.

to the coronavirus family, like SARS-CoV and SARS-CoV-2. Their structures and mechanisms of infection are similar.[9,11]

To date, several studies have documented the correlation between smoking and the incidence of COVID-19.[12-15] In some trials, smokers were more likely (1.4-fold) to show extreme effects of COVID-19 and their mortality risk was around 2.4 times that of non-smokers.[12,14]

The precise duration of smoking is not recorded in most reports. However, we are yet to find a report determining the magnitude of COVID-19 pneumonia in thorax computed tomography (CT) among smokers.

Imaging plays a significant role in COVID-19 pneumonia diagnosis and management. In highly suspected cases, CT is considered the first-line imaging modality and helps detect improvements during treatment.[16,17] It can detect lung lesions quickly at an early stage with high sensitivity.[18] The severity of the lung involvement in CT images can represent the severity of the disease.

The purpose of this research is to investigate the effect of the history of smoking on the severity of COVID-19 radiological findings. We compared the CT severity scores (CTSS) of smoking COVID-19 patients with those of non-smoking COVID-19 patients.

MAIN POINTS

- Significant damage to the lungs from smoking increases the risk of coronavirus disease 2019 (COVID-19) and the development of serious illness.
- Pneumonia among smokers is more severe than never-smokers, according to computed tomography severity scores (CTSS).
- Semi-quantitative CTSS assessment helps assess the extent of the disease in COVID-19 patients and indicates severity.

MATERIAL AND METHODS

Patients and Groups

This study protocol was approved by Haydarpaşa Numune Training and Research Hospital's Medical Ethics Committee and by the Turkish Ministry of Health, COVID-19 Scientific Research Committee (approval number: 62977267-E.75).

We retrospectively evaluated 121 patients with positive reverse transcription-polymerase chain reaction (RT-PCR) results for COVID-19 whose thorax CTs were obtained in our tertiary hospital between May 10, 2020, and November 30, 2020. The inclusion criteria were as follows: (1) initial RT-PCR test performed on admission day, (2) thorax CT imaging performed within 48 hours after RT-PCR testing, and (3) initial CT examination performed within 14 days (early and progressive phase of the disease) after the onset of initial symptoms.[19] Being under the age of 18 years was the exclusion criterion. Patients with comorbid diseases and malignancies were not included in the evaluation. The time between the onset of the patient's symptoms, the date of the first positive RT-PCR test, and the date of the first thorax CT scan were recorded. Forty-seven cases were excluded because the date of clinical onset was uncertain, and 121 remaining patients (15 current smokers, 38 former smokers, and 68 never-smokers) who met the above criteria were included in our study group (Figure 1).

Image Interpretation

Computed tomography was performed using one of the CT scanners of our hospital (General Electric Healthcare Optima CT 520, USA) allocated for patients with suspected COVID-19. The same device was used in all the patients for the initial images, and the images were acquired using the following parameters: 100 kV, 120 mA, detector coverage: 40.0 mm,

helical thickness: 5.0 mm, pitch and speed (mm/rot): 1.531 : 1 and 61.25, respectively, and rotation time: 0.5 seconds. In all patients, CT examinations were conducted without a contrast medium in the supine position. The images were reconstructed using the lung window (width: 1000-1400 HU; level: 750 HU) and the mediastinal window (width: 350 HU; level: 35-40 HU).

Chest Computed Tomography Severity Score Assessment

All CT images were separately checked for the semi-quantitative CT (SCT) study by a board-certified radiologist (BY) with 5 years of experience and a radiologist (AOB) with 17 years of experience at the workstation. Observers were not informed of the experimental results and clinical findings of the patient.

We used CTSS for the assessment of the COVID-19 load on the initial scan received at admission, as defined by Yang et al.[20] This score uses lung opacification as a measure to show the extent of lung involvement. All thin-section CT scans were examined in the lung parenchyma window. The number of lung segments, which was 18, was accepted as 20 in order to facilitate the evaluation and ensure equality. While the posterior-apical segment of the left upper lobe was divided into apical and posterior regions, the anteromedial basal segment of the lower left lobe was divided into anterior and medial basal regions. Dividing the lung into 20 regions allowed us to evaluate both sides symmetrically and equally. No lung opacities or those involving less than 50% or more than 50% of each region were assigned scores of 0, 1, and 2, respectively. The CTSS was defined as the total score given to 20 lung regions, varying from 0 to 40 points.[20] The SCTSS analyses were performed independently and final decisions were made by consensus.

Evaluation of Chest Computed Tomography Features

Two radiologists analyzed all images on a consensus basis for the features mentioned subsequently. The distribution of lesions was classified as central (lesion >3 cm from the pleura), peripheral (closer to the pleura), or both on each CT scan in the involved segments. The lesions were also categorized as unifocal or multifocal and according to attenuation of opacities [the presence of ground-glass opacities (GGO), consolidation, or mix]. Additional findings were also documented, such as the crazy-paving pattern (the thickening of interlobular septum and intralobular lines superimposed with GGO), curvilinear bands, tree-in-bud appearance, air bronchogram sign, air-bubble sign, reversed halo sign (a round GGO focal region surrounded by complete consolidation ring), and bronchiectasis. Coronavirus disease 2019- related other exceedingly rare findings were also investigated, such as cavitation, lymphadenopathy (interpreted as a lymph node with a short axis of at least 1 cm), and pleural effusion. All subjective assessments were carried out in accordance with the thoracic imaging guide.[18,20]

Clinical Classifications

All COVID-19 cases were clinically divided into 4 categories at the time of initial presentation and CT imaging based on clinical, radiological, and laboratory findings as defined by the World Health Organization as follows: the asymptomatic group had no pneumonia findings on CT, the mild group had mild symptoms (weakness, anosmia, etc.) and mild pneumonia in imaging, the common-severe group showed severe symptoms requiring hospitalization, and the severe-critical group had serious respiratory distress, septic shock, respiratory, or other organ failure needing intensive care unit (ICU) admission.[19]

Lymphopenia (<800 μL), the elevation of liver and kidney function tests, high-precision cardiac troponin I, D-dimer (>1000 ng/mL), high lactate, prolonged prothrombin time, decreased fibrinogen, high lactate dehydrogenase, creatine kinase elevation in the presence of inflammatory indicators [C-reactive protein (CRP) (>40 mg/L), ferritin (>500 ng/mL), interleukin-6, etc.] may be considered poor prognostic signs.[19,21]

Statistical Analysis

Statistical analysis was conducted with Statistical Package for the Social Sciences software for Windows, version 25.0. (IBM Corp, Armonk, NY, USA). Descriptive statistical methods (standard deviation, average, rate, percentage, minimum, and maximum) were used to analyze the results. Kolmogorov–Smirnov, Shapiro–Wilk, and graphical tests were utilized to check the suitability of quantitative data to normal distribution. The Student's *t*-test was used for 2-group comparisons of normally distributed quantitative data, while Mann–Whitney *U* test was used for 2-group comparisons of non-normally distributed data. One-way analysis of variance test was utilized for comparison of 3 or more normally distributed groups and Bonferroni test for paired comparisons. Kruskal–Wallis, Bonferroni, and Dunn's tests were used for paired comparisons of 3 or more non-normally distributed groups. Multivariate analysis of covariance (MANCOVA) was used to correct for gender and age differences between groups, where significant effects were observed. The Pearson's chi-square test was used to compare qualitative results. Spearman's correlation analysis was used to assess the relationship among variables. Diagnostic screening assessments (sensitivity, specificity, positive predictive value, and negative predictive value) and receiver operating characteristics curve analysis were used to evaluate the cut-off for CTSS. Significance was assessed at $P < .05$.

The evaluation of the correlation coefficient (*r*) is made according to the following criterion: The *r*-value of 0-0.25 was considered poor, 0.26-0.49 as weak, 0.50-0.69 as moderate, 0.70-0.89 as strong, and 0.90-1.00 as very strong.

RESULTS

This study included 121 patients [76 (62.8%) males and 45 (37.2%) females] with positive PCR test results for SARS-CoV-2. Their ages ranged from 21 to 80 years, with a mean age of 44.17 ± 12.65 years. Fifteen (12.4%) active smokers, 38 (31.4%) former smokers, and 68 (56.2%) never-smokers were included in this study.

We observed a significant difference between the ages of patients who did and did not smoke ($P = .003$ and $P < .001$). Paired comparisons revealed that the mean age of those who formerly smoked was higher than those who actively smoked and those who had never smoked ($P = .021$, $P = .008$, and $P < .05$, respectively) (Table 1).

Table 1. Evaluation of Descriptive Features According to Smoking

	Never-Smokers (n = 68)	Current Smokers (n = 15)	Former Smokers (n = 38)	*P*	Post Hoc
Age (years)					
Median	**42.5**	**39**	**52**	**.003**[**a]	3 > 1.2
Mean ± SD	42.13 ± 11.07	39.47 ± 9.18	49.66 ± 14.76		
Gender (%)					
Female	**54.4%**	**20.0%**	**13.2%**	**.001**[**b]	3.2 > 1
Male	**45.6%**	**80.0%**	**86.8%**		
CT (%)					
Pathological	**57.4%**	**66.7%**	**94.7%**	**.001**[**b]	3 > 1.2
Normal	**42.6%**	**33.3%**	**5.3%**		

[a]One-way ANOVA test; [b]Pearson's chi-square test; [**]*P* < .01.
CT, computed tomography; SD, standard deviation; ANOVA, analysis of variance.

The mean of the initial CT score measurements of males was 6.84 ± 6.50 and that of the females was 3.67 ± 4.73. Males had a higher mean initial CT score measurement than females. The smoking rate was higher among males compared to females (*P* = .001 and *P* < .01). A significant difference was observed between the initial CTSS measurements by gender (*P* = .005 and *P* < .01).

Eighty-five patients (70.2%) had evidence of pneumonia on admission CT and 36 (29.8%) showed no sign of pneumonia. Among 85 patients with pneumonia, 94.7% were former smokers, 66.7% were active smokers, and 57.4% had never smoked. A statistically significant difference was found between the CT results of the cases according to smoking (*P* = .001 and *P* < .01).

Among the 85 patients with evidence of pneumonia in thorax CT, the mean CTSS and standard deviation were 8.02 and 5.812, respectively. Pair-wise comparisons of CTSS in patients with pathological CT scans (n = 85) were performed for smoking status [never-smokers and smokers (current or former)] using Mann–Whitney *U* test, which revealed a significant relationship between CTSS of never-smokers (n = 39) and smokers (n = 46) (*Z* = 2.243, *P* = .025). A statistically significant relationship was found between CT scores of never-smokers (n = 39) and former (n = 36) smokers (*Z* = 2.702, *P* = .007). No statistically significant relationship was found between active smokers (n = 10) with either never-smokers or former smokers (*P* > .05).

As age showed a significant correlation with initial CTSS and there were significant age differences between smoking groups, a MANCOVA analysis was performed to correct for age differences (Table 2). We found age to be a significant covariate for CT score (*P* < .01). The same process was also applied to gender, which was not found to be a significant covariant (*P* = .901, partial ETA squared = 0). Therefore, gender correction was not performed for the final analysis. Age-corrected mean CTSS were calculated for 85 patients with abnormal CT scans (CTSS higher than 0). Pair-wise comparison between age-corrected CTSS of smokers (current and former) versus never-smokers showed a significant mean CTSS difference of 3.03 (95% CI: 0.79-5.26; *P* = .008).

Receiver operating characteristics curve analysis revealed 64% area under the curve (*P* = .023). A CTSS >8 differentiated smokers in our study group with a sensitivity of 52.2% and a specificity of 79.5% (Figure 2).

We observed a significant difference between the D-dimer measurements in terms of smoking status (*P* = .011 and *P* < .05). Paired comparisons revealed that D-dimer measurements of current and former smokers were higher than those of non-smokers (*P* = .008 and *P* < .01). C-reactive protein values of the cases also significantly differed by smoking status (*P* = .001 and *P* < .01): CRP values of the subjects who were former smokers were higher than that of never-smokers (*P* = .001 and *P* < .01), and current and former smokers' CRP values were higher than that of non-smokers (*P* = .001 and *P* < .01). *White Blood Cell*, Neutrophile, and *Lymphocyte* measurements of the patients were similar between the smoker groups (*P* > .05).

Among 121 patients, 34 (28.1%) were asymptomatic, 36 (29.75%) had mild disease, 28 (23.14%) had common-severe

Table 2. Age-Corrected Mean CTSS According to Smoking Groups

	Mean CTSS	Age-Corrected Mean CTSS (Mean age: 47.65)	Standard Error
Never-smokers	6.15	6.38 (95% CI: 4.73-8.02)	0.83
Current smokers	7.80	8.91 (95% CI: 5.61-12.2)	1.66
Former smokers	10.11	9.56 (95% CI: 7.82-11.3)	0.873
Smokers (current and former)	9.61	9.42 (95% CI: 7.91-10.9)	0.759

95% CI; age-corrected means were calculated using MANCOVA for a mean age of 47.65 years.
CTSS, computed tomography severity score; MANCOVA, multivariate analysis of covariance.

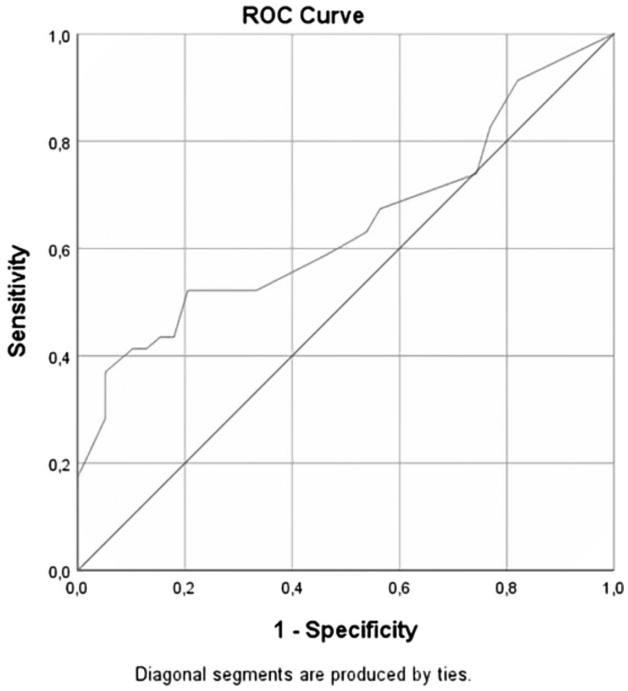


Figure 2. ROC curve for initial CTSS levels according to smoking status. ROC, receiver operating characteristic curve; CTSS, computed tomography severity score.

disease, and 23 (19.0%) had severe-critical disease with severe pneumonia and respiratory distress. Five (14.7%), 16 (44.44%), 14 (50%), and 18 (78.26%) of the patients in these groups were smokers (current and former smokers), respectively.

The CT images of a 52-year-old non-smoker male patient with a mild clinic diagnosis of COVID-19 were demonstrated to be low (Figure 3).

The CT images of a 45-year-old male patient with a common clinic diagnosis of COVID-19 are shown in Figure 4. He had a fever, respiratory symptoms without respiratory distress, and pneumonia in imaging.

Coronal CT images of a 59-year-old former smoker male patient with a severe clinic diagnosis of COVID-19 are also shown in Figure 5. He had a fever, respiratory symptoms with respiratory distress, need for oxygen, and severe pneumonia.

The clinical pictures of patients differed according to smoking status ($P = .001$ and $P < .01$). In the asymptomatic group, the rate of non-smokers was higher than that of former smokers. There were no substantial differences in the mild and common-severe groups. In the severe disease group, the rate of patients who were former smokers was higher than that of never-smokers and current smokers (Table 3). All 4 cases in need of ICU were current or former smokers, and 1 former smoker died.

DISCUSSION

Smoking causes serious lung damage, which raises the risk of COVID-19 and the development of serious illnesses. In our study, smoking status was significantly correlated with thorax CT findings on admission. Semi-quantitative CTSS assessment helps in determining the amount of disease and severity in COVID-19 patients. In age-corrected MANCOVA analysis, smokers had higher age-corrected CTSS compared to never-smokers. Although the means calculated with MANCOVA may be affected by outliers because of the small sample size and slight left skew of the data, it was noted that significant outliers (above third quartile + 1.5 interquartile range) with high CTSS (2 outliers with score = 16) were only present in the never-smokers' group and their removal would not affect the statistical significance of the results. We also performed a rank-based Mann–Whitney *U* test to confirm the significant difference between these groups. The CTSS threshold for differentiating smokers in our study group was 8, with a sensitivity of 52.2% and a specificity of 79.5%.

Of the 121 patients, smokers (current and former) had a higher number of serious cases of COVID-19 than never-smokers in our study. All 4 cases in need of ICU were current or former smokers, and 1 death occurred in the former group. To avoid the confounding effects of comorbidities such as diabetes mellitus and hypertension on COVID-19 pneumonia, we excluded cases with comorbid diseases from our study, which may explain the low mortality rate.

There have been several studies on the effectiveness and usability of CTSS. Yang et al[20] used thorax CTSS to determine the load of COVID-19 at admission. Significant differences were observed between mild and serious cases in terms of lung opacity scored in each lung area ($P < .05$). They

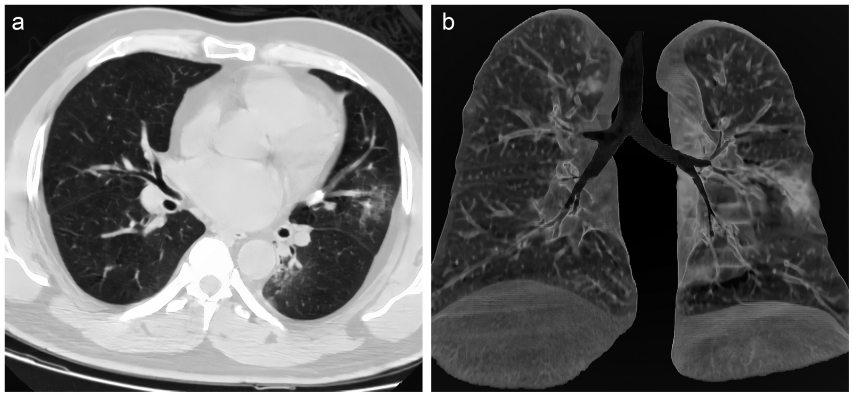


Figure 3. (A) Axial chest CT image shows GGO in the inferior lingular segment of left upper lobe and posterior segment of left lower lobe, CTSS is 4. (B) Volumetric CT image of the same patient shows bilateral and peripheral GGO. GGO, ground-glass opacities; CT, computed tomography; CTSS, computed tomography severity score.

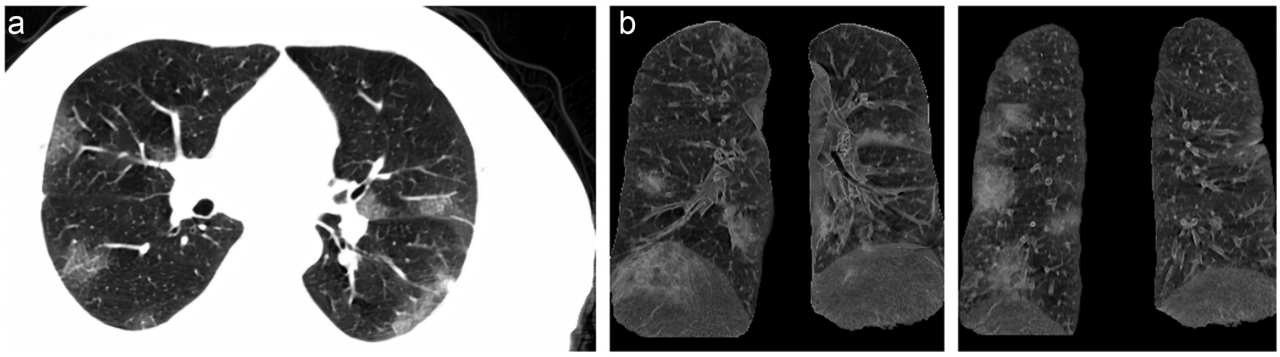


Figure 4. (a) Axial chest CT image shows bilateral, peripheral GGO with less than 50% involvement in all lobes, CTSS is 15. (b) Volumetric CT images of the same patient show bilateral and peripheral GGO. GGO, ground-glass opacities; CT, computed tomography; CTSS, computed tomography severity score.

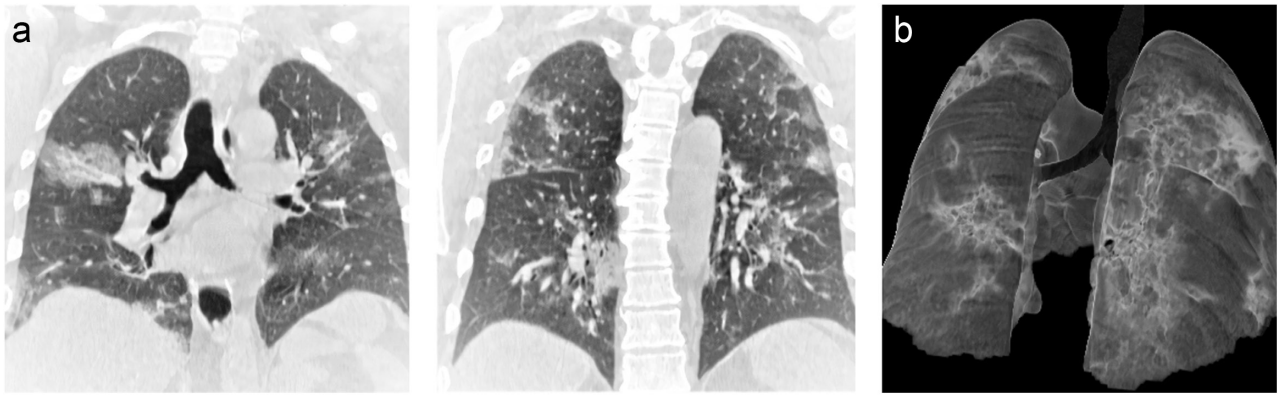


Figure 5. (a) Coronal chest CT images show bilateral, central, and peripheral distribution GGO and consolidation with more than 50% involvement in all lobes, CTSS is 21. (b) Volumetric CT image of the same patient shows bilateral, widespread GGO, and consolidation. GGO, ground-glass opacities; CT, computed tomography; CTSS, computed tomography severity score.

observed that CTSS was higher in serious cases compared to mild cases. They also established that a CTSS threshold of 19.5 could classify serious COVID-19, with a sensitivity of 83.3% and a specificity of 94%, resulting in an Negative Predictive Value of 96.3%.

Several studies on the impact of smoking on COVID-19 and COVID-19 pneumonia have been published.[14] However, we have not seen any research showing the impact of smoking on COVID-19 in terms of thorax CTSS.

Guan et al identified clinical characteristics of patients with COVID-19. There were 1099 smoking patients, 173 with serious symptoms and 926 with mild symptoms. Among severe patients, 16.9% were current smokers and 5.2% were former smokers, while among non-severe patients, 11.8% were current smokers and 1.3% were former smokers. In addition, 25.5% were active smokers and 7.6% were former smokers in the group of patients either in need of mechanical ventilation, ICU admission, or those who died. Among the rest, 11.8% were active smokers and 1.6% were former smokers. No statistical analysis was conducted to assess the relationship between disease severity and smoking status.

Similarly, the clinical characteristics of 140 patients with COVID-19 were presented by Zhang et al.[13] The findings showed that 3.4% of severe patients (n = 58) were active smokers and 6.9% were former smokers; compared with non-severe patients (n = 82), 0% of them were active smokers and 3.7% of them were former smokers, resulting in an OR of 2.233 (95% CI: 0.65-7.63; *P* .2). Smokers had more severe

Table 3. Evaluation of Clinical Status According to Smoking

COVID-19 Severity	Never-Smokers (n = 68)	Current Smokers (n = 15)	Former Smokers (n = 38)	*P*
Asymptomatic	29 (42.6)	3 (20.0)	2 (5.3)	**.001**[**b]
Mild	20 (29.4)	6 (40.0)	10 (26.3)	
Common	14 (20.6)	4 (26.7)	10 (26.3)	
Severe	5 (7.4)	2 (13.3)	16 (42.1)	

[b]Pearson Chi-square test; **$P < .01$.
COVID-19, coronavirus disease 2019.

cases of COVID-19 compared to non-smokers, similar to our study. They had also substantially higher ICU admission and subsequent mechanical ventilation requirement.

In our study, the rates of being symptomatic and hospitalization were higher in COVID-19 cases with a history of smoking. A fatal outcome is more likely to occur among smokers (current and former). In addition, pneumonia in smokers is more severe than never-smokers according to initial CTSS.

There were several limitations to this retrospective study. First, some data were missing because we only had access to clinical and laboratory data from patient files. The sum of pulmonary opacification with CTSS is a visual semi-quantitative assessment. The CTSS suggests that the amount of pulmonary opacification is a substitute for the COVID-19 severity. Furthermore, the findings have not been histologically confirmed.

CONCLUSION

Among COVID-19 patients, smoking is associated with the progression of the disease and increased adverse effects. Semi-quantitative CTSS assessment helps evaluate the disease extent in COVID-19 patients. Also, it is useful for observers and allows consensus.

Ethics Committee Approval: This study protocol was approved by Haydarpaşa Numune Training and Research Hospital's Medical Ethics Committee and by the Turkish Ministry of Health, COVID-19 Scientific Research Committee (Approval number: 62977267-E.75).

Informed Consent: This study was carried out retrospectively using the recorded data of the patients in the health information systems. This submission does not include images that may identify the person.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.Y.; Design – B.Y.; Supervision – B.Y.; Resources – B.Y., A.Ö.B., U.Y.Y.; Materials – B.Y., A.Ö.B., U.Y.Y.; Data Collection and/or Processing – R.B., U.Y.U.; Analysis and/or Interpretation – B.Y., R.B., U.Y.U.; Writing Manuscript – B.Y., A.Ö.B., R.B., U.Y.U.; Critical Review – B.Y., A.Ö.B., R.B., U.Y.U.

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Declaration of Interests: The authors have no conflict of interest to declare.

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Original Article

Is There Any Relationship Between the Number of COVID-19 Tests by Country with the Income Inequality of Countries? A Comparison with Income Inequality Metrics

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Abstract

OBJECTIVE: Coronavirus diseases 2019 test numbers vary from country to country. The present study aims to investigate whether there is a relationship between the number of coronavirus diseases 2019 tests by country with the income inequality of countries.

MATERIAL AND METHODS: The association between the number of coronavirus diseases 2019 tests and income inequality metrics was evaluated in 197 countries. Income inequality metrics consisted of the gross domestic product per capita, Gini index, the P80/P20 ratio, human development index ranking, and poverty rate. The share of the tests that gave positive results (positive rate) and fatality rates was calculated by countries.

RESULTS: There was a strong positive correlation between the number of coronavirus diseases 2019 tests per million people and the number of coronavirus diseases 2019 patients per million people (rho = 0.697, $P < .001$). A significant correlation was observed between the number of coronavirus diseases 2019 tests and all income inequality metrics ($P < .001$). The strongest positive correlation with the number of coronavirus diseases 2019 tests was between gross domestic product per capita (rho = 0.775), while the strongest negative correlation with the number of coronavirus diseases 2019 tests was between human development index ranking (rho = −0.836). The multiple regression analysis showed that age ($P = .01$), gross domestic product per capita ($P < .001$), and human development index ranking were independent factors affecting the number of coronavirus diseases 2019 tests per million people (adjusted $R^2 = 0.301$). The fatality rate was associated with the number of coronavirus diseases 2019 tests ($P = .01$).

CONCLUSION: Income inequalities in countries are associated with the number of coronavirus diseases 2019 tests. For this reason, many deaths from coronavirus diseases 2019 may have gone overlooked in countries with poor-income inequality metrics.

KEYWORDS: SARS-CoV-2, polymerase chain reaction testing, countries, income inequality metrics
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INTRODUCTION

Worldwide, more than 90 million people have caught the coronavirus diseases 2019 (COVID-19) by January 2021.[1] The COVID-19 polymerase chain reaction (PCR) test is accepted as the golden standard method for confirming COVID-19. However, the number of test-positive cases depends on the timing of the outbreak and public health policies between countries.[2] Thus, it is difficult to interpret basic differences in the number of cases between continents. It is known that countries need to do more testing to be able to properly monitor the spread of the virus. Moreover, the number of conducted COVID-19 tests may affect the number of test-positive cases.[3] Health care workers rely on the results to guide patients' medical treatment. On the other hand, individuals rely on test results to decide on whether to self-isolate. Therefore, the small number of tests causes real patients to be ignored, and consequently, the transmission chain cannot be broken and the burden on the health system increases.

It is well-known that the majority of COVID-19-related deaths have occurred in the community where testing capacity is lacking.[4] A lot of patients who died in countries are not able to test, despite presenting with typical symptoms of COVID-19. Therefore, it can be said that COVID-19 cases were under-reported because testing was rarely done, not because COVID-19 was rare. The social quality of the state, the level of democracy, the level of income inequality, poverty and education level, racial/ethnic minority ratio, and the immigrant/refugee population ratio are known to contribute to this.[5] The class inequality of COVID-19 has shown itself both between regions and countries.[6] Both the number of tests per million people (pmp) and non-pharmaceutical public health practices differ from country to country. As an illustration, in South Sudan, where the per capita income is 302 dollars, the number of PCR tests performed pmp is 7000, whereas, in Luxembourg, where the per capita income is 114 000 dollars, this number is 2.7 million (385 times more tests).[7]

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Table 1. The Definitions Regarding Income Inequality Metrics

Income Inequality Metrics	Definitions
Gross domestic product[11]	The total monetary or market value of all the finished goods and services produced within a country's borders in a specific time period
Gross domestic product per capita[11]	Breaks down a country's economic output per person and is calculated by dividing the GDP of a country by its population
P80/P20 ratio[11]	The ratio of the household income at the 80th percentile (i.e., 20% below the wealthiest household) to the household income at the 20th percentile (i.e., 20% above the lowest income household)
Gini coefficient (index)[12]	A measure of statistical dispersion intended to represent the income inequality or wealth inequality within a nation or any other group of people
Human development index[13]	The geometric mean of normalized indices for each of the 3 dimensions that were a long and healthy life, being knowledgeable, and having a decent standard of living
Human development index ranking[13]	A list of countries by inequality-adjusted human development index
Extreme poverty rate[14]	People living on less than $1.25 a day

To the best of our knowledge, there is no study investigating the relationship between income inequality metrics and the number of COVID-19 tests, the number of COVID-19 deaths/patients pmp, and mortality among COVID-19 patients.[8,9] In the present study, the effect of income inequality on the number of COVID-19 tests in countries was investigated with income inequality metrics.

MATERIAL AND METHODS

Total numbers of PCR-positive cases and deaths by COVID-19 reported from all countries (n = 211) worldwide were downloaded from the webpage of the World Health Organization (WHO) on January 10, 2021.[10] Because the total number of tests is often volatile from time to time, it was accepted as 10 months rolling average. Countries with a total number of tests pmp (n = 14) unknown were excluded in the present study. Since countries have performed different testing policies and have a different number of populations, aiming to investigate the state of the current COVID-19 by analyzing the number of test-positive cases alone may lead to bias. Thus, it has been also focused in the current study on changes in the number of test-positive patients and deaths adjusted by the population of each country and considering the timing of the pandemic. The number of population-adjusted total test-positive cases and the number of population-adjusted total deaths were calculated for a population of a million. However, it should be noted that the number of test-positive cases analyzed in this study was smaller than the number of infected people and was observed only after the hidden phase.

The rate of PCR tests among the population (named as examination rate) and the rate of COVID-19-related deaths among the population caught COVID-19 (named as fatality rate) were also calculated. The fatality rate was defined as the number of deaths in persons who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) divided by the number of SARS-CoV-2 cases.

Also, the share of tests that gave positive results (positive rate) and how many tests were performed to find one case of COVID-19 were determined.

Income Inequality Metrics Used in the Present Study

The definitions regarding income inequality metrics are shown in Table 1.

Speculatively, it was suggested that, in developed countries, strict compliance to social distancing is better achieved. Therefore, the gross domestic product (GDP) and GDP per capita of each country were accepted as predictor variables in the present study.

Besides, several variables have been analyzed to determine the effect of income distribution inequality in countries on COVID-19. One of the approaches developed to examine income distribution is to compare the shares of the groups in the population with the highest income and lowest income in the total income. In this comparison, the income of the richest 20% of the population is proportioned to the income of the poorest 20% that is called the P80/P20 ratio. It is accepted that as this ratio increases, the income inequality in the country increases.

Another indicator that measures the inequality in income distribution is the Gini coefficient. This coefficient varies between 0 and 1, and the coefficient is 0 in the case of complete income equality and 1 in the case of complete income inequality. In other words, the closer the Gini coefficient is to 1, the results indicate income inequality.

MAIN POINTS

- The number of coronavirus diseases 2019 (COVID-19) patients detected increases in line with the increase in the number of COVID-19 tests.
- Income inequality in countries determines the number of COVID-19 tests.
- Countries with poor-income inequality metrics may have experienced more COVID 19 deaths.

In this study, the P80/P20 ratios[11] published by the United Nations Development Program (UNDP) for all countries of the world every year, and the Gini index[12] published by The World Bank for all world countries were used.

Moreover, the human development index (HDI) and HDI ranking, which are other indicators of inequality, were examined in the study. A list of countries by inequality-adjusted human development index was published by the UNDP in its 2019 Human Development Report.[13]

The extreme poverty rate, another indication of inequality within and between countries, was obtained from UNDP and The World Bank database.[14,15]

In case there is no data for the year 2020 for each data set, the most recently published data were taken into consideration.

Other Variables Used in the Present Study

By countries, the mean age, the rate of people over 65 years of age, smoking rate, cardiovascular disease-related mortality rate, diabetes mellitus (DM) prevalence, life expectancy, and the number of hospital beds per thousand people were examined.

Statistical Analysis

The data were entered into the Statistical Package for Social Sciences 23.0 (IBM SPSS Corp.; Armonk, NY, USA) package program. Descriptive statistics were used to summarize pertinent study information. Variables were characterized using mean, maximum (max), and minimum (min) values, and percentages were used for qualitative variables. Correlation analysis between numerical variables was performed by Spearman's correlation test, and correlation coefficient (rho) was calculated. If the correlation coefficient was negative, it was accepted as an inverse relationship between 2 variables (an increase in one and a decrease in the other), whereas, if it is positive, it was accepted as a straight relationship (an increase in one and an increase in the other) between the 2 variables. If the rho coefficient is between 0.01 and 0.19, 0.20 and 0.29, 0.30 and 0.39, 0.40 and 0.69, or is ≥0.70, it was accepted as "negligible relationship, weak relationship, moderate relationship, strong relationship, very strong relationship," respectively. Moreover, multivariate regression analysis was done for the relationship between the income inequality metrics with the number of COVID-19 tests per million people. In the present study, since there may be high correlations between the income inequality metrics, multiple regression analysis was performed separately for each income metric. A P value of <.05 was considered statistically significant.

RESULTS

One hundred ninety-seven countries were included in the present study. The numbers and rates of COVID-19 test and COVID-19-related results are shown in Table 2. The mean number of the COVID-19 tests pmp was 335.329, whereas the mean number of PCR-positive patients in pmp was 18.761. An average of 335 people pmp around the world had died because of COVID-19. Examination rate was 33.6% (min: 0.5%, max: 425.4%) whereas the mortality rate of patients with COVID-19 was calculated as 1.8% (min: 0%, max: 28.8%).

The share of test-positive cases differed significantly from country to country (P < .001) (Figure 1). The positivity rate was 9.6% on average (min: 0.4%, max: 65.4%). The worldwide performed test median per case was 12.6. While this number remained below 3.5 in countries such as Argentina, Mexico, Bolivia, Costa Rica, Ecuador, and Brazil, it was over 500 in countries such as China, Vietnam, New Zealand, and Hong Kong.

The relationships between the number of COVID-19 tests and the variables were shown in Table 3. There was a strong positive correlation between the number of COVID-19 tests and GDP per capita (rho = 0.775, P < .001), whereas there was a strong negative correlation between HDI ranking and the number of COVID-19 tests (rho = −0.836, P < .001). Increase in the countries' Gini coefficient, extreme poverty rate, and P80/P20 ratio was associated with a decrease in the number of COVID-19 tests pmp (negative correlation). The number of COVID-19 tests pmp was moderately correlated with the age and the rate of the population over 65 years of age (rho = 0.715 and rho = 0.636, respectively). The number of COVID-19 PCR tests pmp was weakly associated with smoking rate, and GDP (rho = 0.197 and rho = 0.197, respectively). In the multiple regression analysis, age (P = .01), GPD per capita (P < .001), and HDI ranking were found to be independent factors affecting the number of COVID-19 PCR tests pmp (adjusted R^2 = 0.301).

Table 2. The Numbers and Rates of COVID-19 Test and COVID-19-related Results

Variables	Mean ± SE	Median Values (IQR)
The COVID-19 tests pmp, n	345 815 ± 43 406	149 192 (371 174)
PCR-positive patients in pmp, n	19 828 ± 1586	12223 (29391)
People who died from COVID-19 in pmp, n	335.1 ± 29.8	157.0 (448.2)
Examination rate, %	33.6 ± 4.1	14.2 (33.6)
The mortality rate of patients with COVID-19, %	1.8 ± 0.1	1.5 (1.4)
The positivity rate, %	9.6 ± 0.6	7.9 (11.0)
The performed test per case, n	85.6 ± 18.4	12.6 (34.0)

Pmp; per million people, n; number, SE; Standard error, IQR; interquartile range; PCR, polymerase chain reaction.

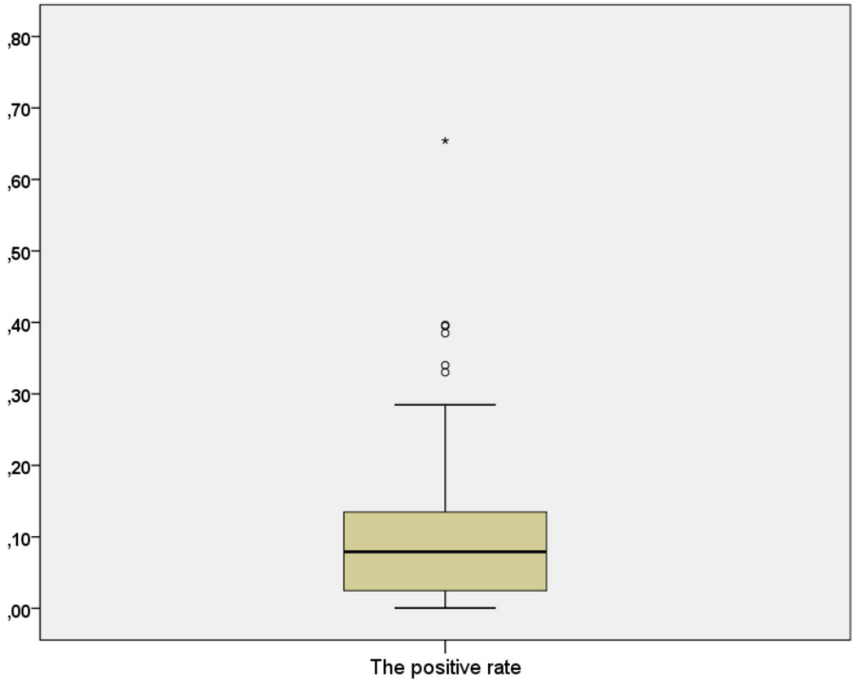


Figure 1. The analysis of number of test-positive cases by countries.

A strong positive correlation was found between the number of COVID-19 tests and the number of COVID-19 patients pmp (rho = 0.697, $P < .001$). It was observed that as the number of test increased, the number of patients increased (Figure 2).

The number of COVID-19 patients pmp was positively correlated with the mean age in countries (rho = 0.533, $P < .001$), the rate of people over 65 years (rho = 0.540, $P < .001$), smoking rate in the population (rho = 0.272, $P < .001$), cardiovascular disease (CVD)-related mortality rate (rho = 0.240, $P = .002$), DM prevalence (rho = 0.172, $P = .02$), and the number of hospital beds per thousand people (rho = 0.440, $P < .001$).

The number of COVID-19-related deaths pmp was positively significantly related with the mean age of countries, the rate of people over 65, CVD-related mortality rate, the number of hospital beds per thousand people, examination rate, GDP, GDP per capita, and life expectancy in countries, although it was negatively significant associated with the Gini coefficient, extreme poverty rate, HDI ranking, and P80/P20 ratio (Table 4).

The fatality rates in the countries were found not to be associated with any variables other than the examination rate (Table 4). There was also a weak negative correlation between examination rate and fatality rate (rho = −0.181, $P = .01$).

Table 3. Univariate Spearman's Rank-Order Correlation Analysis Between the Variables with the Number of COVID-19 Tests Per Million People and Multivariate Regression Analysis

	The Number of COVID-19 Tests Per Million People		Multivariate Analysis	
Variables	**rho Coefficient**	***P***	**Standardized Coefficients Beta**	***P***
Age	0.715	<.001	0.465	.01
Rate of people over 65 years of age	0.636	<.001	−0.017	.925
Smoking rate	0.197	.006	−0.053	.570
Gini coefficient	−0.366	<.001	−0.109	.925
GDP	0.197	.007	−0.121	.439
GPD per capita	0.775	<.001	0.710	<.001
Extreme poverty rate	−0.756	<.001	−0.036	.743
Life expectancy	0.759	<.001	0.058	.579
HDI ranking	−0.836	<.001	−0.866	<.001
P80/P20	−0.337	<.001	−0.025	.750

GDP, gross domestic product; HDI, human development index; P80/P20, calculated as the ratio of total income received by the 20% of the population with the highest income (the top quintile) to that received by the 20% of the population with the lowest income (the bottom quintile).

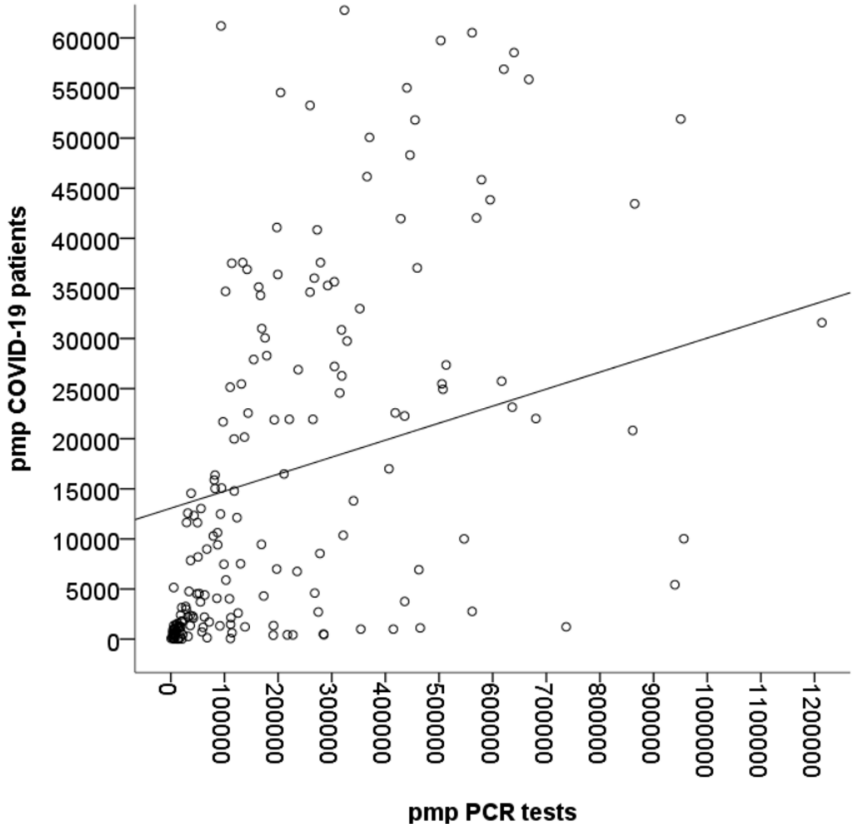


Figure 2. The correlation between the number of COVID-19 tests and the number of COVID-19 patients (rho = 0.697, $P < .001$). COVID-19, coronavirus disease 2019. pmp; per million people.

When countries are grouped as countries with a positivity rate of less than 1% (low positive rate, n = 23) and a positivity rate higher than 20% (high positive rate, n = 29), the number of COVID-19 patients pmp ($P < .001$), the number of COVID-19-related deaths pmp ($P < .001$), and fatality rate ($P < .001$) were higher in countries with a high positivity rate.

DISCUSSION

The number of confirmed patients infected with COVID-19 is what informs about the development of the pandemic. However, the confirmation of a case is based on a test. The WHO defines a confirmed case as "a person with laboratory confirmation of COVID-19 infection".[16] The focus of the current study was on using testing data to help properly interpret the data on confirmed cases and deaths. In the present study, a global data set on COVID-19 testing on the building was focused. The current study has detected a strong correlation between the number of COVID-19 tests and the number of confirmed COVID-19 cases. This means that the number of confirmed cases depends on how much a country performed tests. Without testing, there are no data and no way to understand the pandemic. It can be said that testing is a window into the pandemic and how it is spreading, and without data on who is infected by the virus, there is no way of understanding the pandemic.

One important way to understand if countries are testing sufficiently is to look at the share of tests returning a positive result—known as the positive rate. The WHO suggested that a positive rate should be around 3-12% as a general benchmark of adequate testing.[17] The mean positive rate was 9.6% in all countries, and enormous differences across countries were seen. Some countries like China, Vietnam, Hong Kong, New Zealand, Australia, Cuba, and Taiwan have a positive rate of less than 1% although others such as Mexico, Argentina, Bolivia, and Brazil have positive rates of 25-50% or even more. In these countries, a case is found for every few tests conducted. In countries with a very high positive rate, it is unlikely to be testing widely enough to find all cases. As stated above, it is known that countries with a positive rate of less than 1% protect their citizens better from the pandemic than countries with positive rates of 25-50% or even more. In the present study, it was determined that countries with low-positive rates had a fewer COVID-19 patients pmp ($P < .001$), fewer COVID-19 deaths ($P < .001$), and a fewer fatality rate ($P < .001$) than those with high-positive rates.

Another way of looking at the extent of testing relative to the scale of the pandemic ask how many tests a country performs to find one COVID-19 patient. This question is simply the inverse of the present data on the positive rate. Countries that performed very few tests per confirmed case are unlikely to be testing widely enough to find all cases.[17] It has been suggested that between 10 and 30 tests per confirmed case as a general benchmark of adequate testing by the WHO. The worldwide test median per confirmed case was 12.6, and this number varied enormously between countries.

In the current study, it was determined that these differences are caused by income inequality in countries. A strong positive correlation was found between the number of

Table 4. Relationships Between the Number of COVID-19-Related Deaths pmp, Fatality Rate, and Variables

	COVID-19-Related Deaths pmp		Fatality Rate*	
Variables	rho Coefficient	*P*	rho Coefficient	*P*
Age	0.520	<.001	-0.020	.778
Rate of people over 65 years of age	0.550	<.001	0.115	.138
Smoking rate	0.289	<.001	0.154	.031
CVD mortality rate	0.180	.022	0.006	.941
DM prevalence	0.105	.173	−0.131	.101
Hospital beds (per thousand people)	0.406	<.001	−0.052	.519
Examination rate	0.539	<.001	−0.181	.011
Gini coefficient	−0.225	.006	0.037	.647
GDP	0.276	<.001	0.101	.118
GPD per capita	0.465	<.001	−0.098	.199
Extreme poverty rate	−0.458	<.001	0.075	.382
Life expectancy	0.482	<.001	−0.048	.514
HDI ranking	−0.545	<.001	0.033	.670
P80/P20	−0.236	.004	0.003	.968

*It was calculated as the number of COVID-19-related deaths/the number of COVID-19 patients.
CVD, cardiovascular disease-related; DM, diabetes mellitus prevalence; GDP, gross domestic product; HDI, human development index; P80/P20, calculated as the ratio of total income received by the 20% of the population with the highest income (the top quintile) to that received by the 20% of the population with the lowest income (the bottom quintile).

COVID-19 tests and GDP per capita whereas a strong negative correlation was detected between HDI ranking and the number of COVID-19 tests. Besides, the increase in the countries' Gini coefficient, extreme poverty rate, and P80/P20 ratio was associated with the decrease in the number of COVID-19 tests. In countries with high-income inequality, less testing has been performed. In a study that investigated the success of containment, it was concluded that the containment rate is explained by GDP alone.[9]

Naturally, in countries where the number of tests is low, both the number of COVID-19 patients pmp and the number of COVID-19-related deaths pmp have been lower. On the other hand, the reason for this is under-ascertainment. The absence of comparable pandemics in many African countries is notably perplexing although the pandemic has strained health systems to near-capacity in many high-income countries.[18] Under-reporting of COVID-19 deaths is a likely explanation of these patterns; however, it is difficult to measure given that vital registration systems and excess mortality data are absent in many countries.[19] The "Africa paradox" that was called why COVID-19 would not spread as efficiently in Nairobi, Accra, or Lagos as it has in New York City, London, or Mumbai has may explain with insufficient data.[20] In September, in a published report, it was estimated that only 1 in 80 deaths due to COVID-19 have likely been reported in Damascus, Syria.[21] In another report, the authors estimated there were 16 090 (95% CI: 14 300–17 990) undetected COVID-19 deaths from April to November in Khartoum, Sudan.[21] In a systematic post-mortem surveillance study in Africa, it was observed that the impact of COVID-19 in Africa has been vastly underestimated.[20,22]

It was observed that the fatality rate was not affected by the income inequality of the countries, although countries with income inequality had fewer COVID-19-related deaths than countries with less income inequality (Table 4). That made think that the disadvantaged classes such as workers, poor people, and refugees in the country could not be tested, and their COVID-19-related deaths were not recorded, that the advantageous classes could get tested and even if they live in a poor-income country, they are at risk of death only as much as those living in the rich country.

It is well known that, among the countries, it is not the richest societies that have the best health, but those which have the smallest income inequality differences between rich and poor.[23] It is suggested that income inequalities could be a predictor for the investment in, and popular support of, public services.[24] It is also known that countries that had income equality are made better use of public resources, whereas the combination of poverty and poor public health contributes to both the number of COVID-19 tests and the number of COVID-19 cases and deaths. In a study that investigated the distribution of tests for COVID-19 across income levels, it was observed that COVID-19 tests are almost perfectly distributed across income groups in New York City.[25] In Toronto, the 20 neighborhoods with the highest minority proportion and lowest household income population and the 20 neighborhoods with the lowest minority proportion and highest household income population were found to have differences in the number of tests per thousand people.[26] Countries with a more even distribution of income have a stronger sense of the public sector, with well-funded safety nets and services.[27,28] It may say that countries with poor income inequality metrics, therefore, have big network of laboratories for testing and a strong federal public health network, and these countries were accepted as successful countries in pandemic crises. They are also known to do more testing. This may suggest that countries with low levels of income inequality were simply more prepared and were in a stronger position to cope with the COVID-19 crisis.[27] There were some limitations. First, the total number of people infected with COVID-19 all over the world is not known. All it was known is the infection status of those who have been tested. Second, the indications of COVID-19 tests are not the same in each country. On the other hand, while some countries may report the number of people tested, others report the number of tests. Besides, some countries report their testing data in a way that leaves it unclear what the test count refers exactly. Third, confusion continues over whether people die "of" COVID-19 or "with" COVID-19. What defines a COVID-19 death? The answer remains still complicated, and the debate about

the COVID-related death counts continues. Many scientists still doubt the official totals. Data on excess deaths may suggest coronavirus death tolls are likely an underestimate. In April 2020, the WHO states that "a death due to COVID-19 is defined for surveillance purposes as a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID disease," and European Centre for Disease Prevention and Control later on also adopted these inclusion criteria in May 2020.[29,30] However, it should be noted that there are still many differences among countries about the COVID-related death definition. Although strict compliance to social distancing is better achieved in developed countries was suggested, some countries, such as Sweden, are examples that do not fit this.

In conclusion, regarding the increase in the number of COVID-19 tests, the number of COVID-19 patients detected is increasing. Income inequality in countries determines the number of COVID-19 tests. Since income inequality in countries affects COVID-19 test numbers, many COVID-19-related deaths may be overlooked in countries with poor-income inequality metrics.

Ethics Committee Approval: The Institutional Review Board of institutions approved the data analyses, and ethics committee approval was not necessary obtained for the present study as it was an internet-based study.

Informed Consent: Not applicable since the present study was an internet-based study.

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Original Article

Charlson Comorbidity Index in Predicting Poor Clinical Outcomes and Mortality in Patients with COVID-19

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Abstract

OBJECTIVE: As known, older age and comorbidities are associated with poor clinical outcomes in patients with coronavirus disease 19. The aim of this study was to investigate the effect of the Charlson Comorbidity Index in predicting poor clinical outcomes in coronavirus disease 19 patients.

MATERIAL AND METHODS: Demographic characteristics and poor clinical outcomes (presence of pneumonia, respiratory failure, intensive care unit admission, and mortality) of the patients were evaluated retrospectively. Classical and modified Charlson Comorbidity Index was calculated and adjusted according to age.

RESULTS: In this study, 106 women and 107 men were included. The comorbidity rate was 50.7% and the most common comorbidities were hypertension (21.6%) and diabetes mellitus (15%). The rates of respiratory failure, intensive care unit admission, and mortality were 15%, 2.3%, and 2.8%, respectively. Older age was a high risk for poor outcomes. Pneumonia (odds ratio: 6.6; 95% CI: 3.4-12.7), respiratory failure (odds ratio: 5.2; 95% CI: 2.03-13.2), and intensive care unit admission (odds ratio: 1.1; 95% CI: 1.01-1.1) were significantly higher in patients with comorbid diseases than patients without any comorbidity ($P < .05$). Both median-modified and classical Charlson Comorbidity Index and their age-adjusted scores were significantly higher in patients with poor outcomes.

CONCLUSIONS: It is suggested that evaluation of the Charlson Comorbidity Index might contribute to the management of the patients with coronavirus disease 19 by predicting risk group for poor clinical outcomes and mortality.

KEYWORDS: COVID-19, comorbidity, Charlson Comorbidity Index, mortality, clinical outcome
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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 is a novel virus that causes coronavirus disease 2019 (COVID-19) which has been responsible for the global pandemic since March 2020. According to World Health Organization (WHO) report, there have been 203 174 401 confirmed cases of COVID-19, including 4 304 114 deaths until August 08, 2021.[1] From March 2020, when the first case was identified in our country, to August 2021, 5 895 841 cases were diagnosed and 52 088 people died.[2]

Coronavirus disease has a wide clinical spectrum from asymptomatic to severe disease including acute respiratory distress syndrome (ARDS) and death.[3] Mortality is a major concern of all clinicians in all countries.[4] The pathogenesis of COVID-19 infection remains unclear and there is no specific treatment protocol. Therefore, the management of COVID-19 and its outcomes are based on supportive therapy. Clinicians have been fighting against this new and unknown virus since the first day and are seeking to improve survival and outcomes in severe diseases.[5] To know the risk factors of worse clinical outcomes and mortality can help us to define the patients with COVID-19 at higher risk and to plan specific approach for prevention of serious events.[4,5]

Older age and comorbidities are the main risk factors of severe COVID-19 disease.[1] Most of the previous studies have identified comorbidities such as hypertension (HT), diabetes mellitus (DM), coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD), cancer, and chronic renal disease (CRD) as the high-risk factors.[6,7]

Charlson Comorbidity Index (CCI) is a validated index that calculates the comorbidities and predicts the risk of death within 1 year of hospitalization.[8] It is found that CCI score above 0 was associated with an increased risk of severe disease and death when controlled for age and sex.[9] The aim of this study was to investigate the effect of CCI in predicting poor clinical outcomes such as pneumonia, respiratory failure, intensive care unit (ICU) admission, and mortality in patients with COVID-19.

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MATERIAL AND METHODS

Medical records of all hospitalized patients who were diagnosed with COVID-19 between March and June 2020 were evaluated retrospectively. The definitions of the COVID-19 disease were based on the WHO COVID-19 case definition sheet. While the presence of a positive nasopharyngeal polymerase chain reaction (PCR) test was defined as a definite case, cases with similar clinical and radiological findings (multiple ground-glass opacities, with peripheral and lower lung distribution) were defined as high probable COVID-19 despite the negative nasopharyngeal PCR test result.[10] Thorax CT scans of all patients with COVID-19 (both definite and high probable) were examined by the same radiologist who is specialized in thoracic radiology.

Inclusion criteria were as follows:

- to have definite COVID-19 infection (with positive nasopharyngeal PCR result),
- to have high probable COVID-19 infection (clinical and radiological findings are compatible with COVID-19, but at least 2 PCR tests performed 24-48 hours apart are negative), and
- hospitalization due to COVID-19 infection.

Exclusion criteria were as follows:

- to be followed up in outpatient clinic with the diagnosis of definite or high probable COVID-19 infection and
- hospitalization due to non-COVID-19 diseases.

Demographic characteristics including body mass index (BMI), smoking history and comorbidities, clinical outcomes such as the presence of pneumonia, respiratory failure, ICU admission, and mortality were recorded. Respiratory failure was defined as oxygen saturation (SO_2) less than 90% in room air at the time of admission or during follow-up.

The CCI is a simple, easy-to-perform, and valid method to estimate the risk of death related to comorbid diseases.[8] Classical CCI includes 19 medical conditions weighted 1-6 with total scores ranging from 0 to 33. Furthermore, age-adjusted CCI score can be calculated by adding 1 point for each decade of age over 40 years. Modified CCI, on the other hand, is a simpler form that includes 12 comorbid conditions with a total score weighted from 0 to 24. Age-adjusted score can also be calculated by adding 1 point per decade over the age of 50.[8,11-13] Definitions and items of classical and modified CCI are shown in Table 1.

Table 1. Calculation of Classical and Modified Charlson Comorbidity Index Scores and Age-Adjusted Scores

Comorbid Conditions	CCI Score	Modified CCI Score
Age		
<40	+0	–
<50	–	+0
41-50	+1	–
50-59	–	+1
51-60	+2	–
60-69	–	+2
61-70	+3	–
70-79	–	+3
≥71	+4	–
>80	–	+4
Myocardial infarction	1	0
Congestive heart failure	1	2
Peripheral vascular disease	1	0
Cerebrovascular disease	1	0
Dementia	1	2
Chronic pulmonary disease	1	1
Rheumatic disease	1	1
Peptic ulcer disease	1	0
Mild liver disease	1	2
Diabetes without chronic complication	1	0
Diabetes with chronic complication	2	1
Hemiplegia	2	2
Renal disease	2	1
Any malignancy without metastasis	2	2
Leukemia	2	
Lymphoma	2	
Moderate or severe liver disease*	3	4
Metastatic solid tumor	6	6
AIDS (exclude asymptomatic infection)**	6	4
Max. comorbidity score	33	24
Max. age-adjusted comorbidity score	37	28

*Liver disease: mild, chronic hepatitis or cirrhosis without portal hypertension; moderate, cirrhosis, portal hypertension; severe, portal hypertension, history of variceal bleeding.
**AIDS: current CD4 count <200, opportunistic infection in the last 1 month, active AIDS such as Kaposi sarcoma.
AIDS, acquired immunodeficiency syndrome.

MAIN POINTS

- Older age and comorbidities were associated with poor clinical outcomes in patients with coronavirus disease 19.
- Charlson Comorbidity Index (CCI) is a tool for calculating comorbidity scores using a predefined list of medical conditions and also it can be adjusted for age and was associated with mortality.
- It is thought that evaluating the CCI score during the initial admission will contribute to the identification of the risky group and the preparation of an early action plan.

In this study, comorbidities were recorded from medical data. Classical and Modified CCI (cCCI and mCCI) were calculated for each patient. In addition, both scores of the cCCI and mCCI were adjusted and re-calculated according to age. Furthermore, CCI scores were classified according to the total

score as follows: 0 point: no comorbidity, 1-2: mild, 3-4: moderate, and ≥5: severe.[9]

Our study was approved by the Ministry of Health Scientific Research Board and Kocaeli University Non-Interventional Research Ethics Committee with the number GOKAEK-2020/11.19. As informed consent from patients to review their medical records was not obtained, patient data were de-identified. The flowchart of the study is presented in Figure 1.

Statistical Analysis

Statistical Package for the Social Sciences Statistics 20.0 (SPSS Inc.; Chicago, IL, USA) package program was used for statistical analyses of the study. Categorical variables were expressed as counts (percentage). Continuous variables were expressed as median or mean ± standard deviation. Mann–Whitney *U* test was used for the comparison of continuous variables. Comparisons of categorical variables between the groups were performed using the chi-square test. The risk was calculated by the chi-square test. A 2-sided *P* value <.05 was considered statistically significant.

RESULTS

Totally 213 patients with COVID-19 were included in the study; 106 women (49.8%) and 107 men (50.2%). The median age and BMI of the study population were 46 years (min: 18, max: 93) and 25.5 kg/m^2 (min: 17, max: 47.2), respectively. Among the study population, 46.7% of the patients had a smoking history, 20.7% was current smoker, and 26% was former smoker. Coronavirus disease19 PCR test was positive in 69.5% of the patients. At initial admission, 5.3% of the patients had room air SO_2below 90%. Mean SO_2 was 95.98 ± 3.3% during first admission, and the mean duration of hospitalization was 4.99 ± 3.2 days. During follow-up, 15% of the patients had respiratory failure. The need for ICU rate was 2.3% and the mortality rate was 2.8%. Demographic characteristics, CCI scores of the study population, and clinical outcomes of the disease are shown in Table 2.

The comorbidity rate was 50.7% and the most common comorbidities were HT (21.6%), DM (15%), and malignancy (8.5%) (Figure 2). Although the presence of the comorbidity was significantly higher in men than women (57.9% vs. 43.4%, *P* = .03), clinical outcomes of the disease were similar between the gender.

The study population was categorized by age. Patients over 65 years old were defined as elderly and 26.8% of the study population were elderly. The frequency of comorbidities (37.2% vs. 87.7%, *P* = .001) and poor clinical outcomes such as pneumonia (58.3% vs. 87.7%, *P* = .001) and respiratory failure (9.7% vs. 29.8%, *P* = .001) were significantly higher in

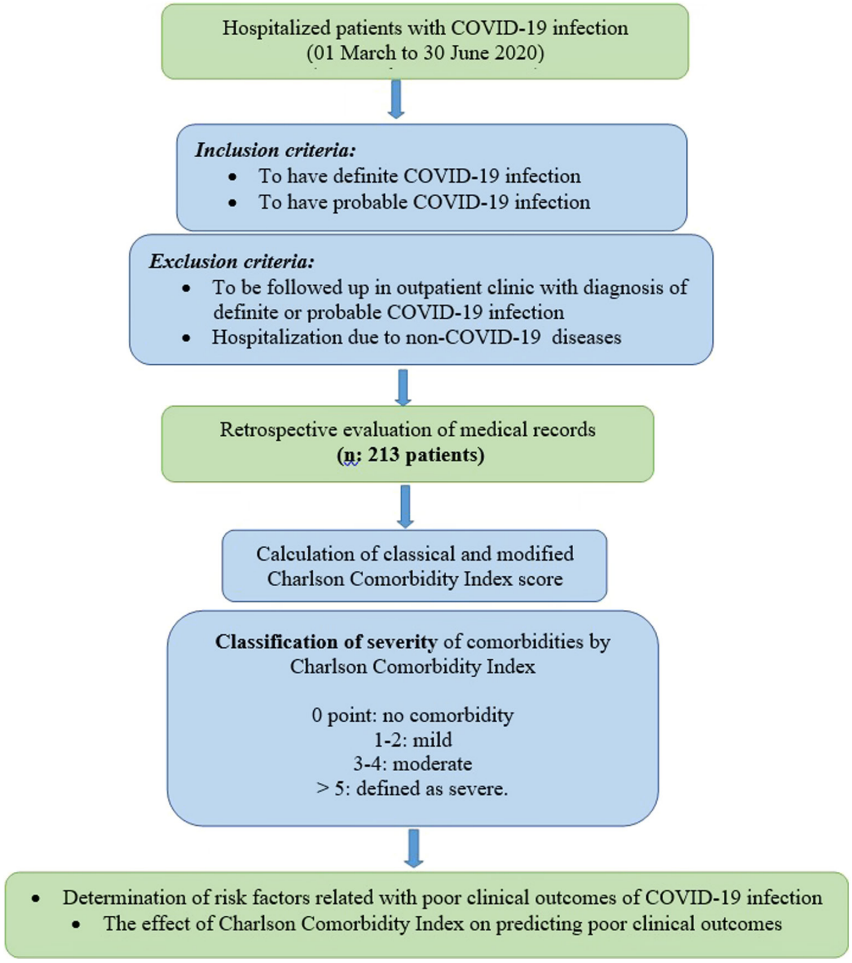


Figure 1. Flowchart of the study.

Table 2. Demographic Characteristics and CCI Scores of the Patients

	Variables	n(%)
Gender, n (%)		
Women		106 (49.8)
Men		107 (50.2)
Age category, years, n (%)		
<65		156 (73.2)
≥65		57 (26.8)
BMI category, kg/m^2, n (%)		
<18	Cachexia	2 (1.3)
18-25	Normal weight	66 (41.5)
25-30	Over weight	60 (37.7)
>30	Obese	24 (15.1)
>40	Morbid obese	7 (4.4)
Smoking history, n (%)		
Non-smoker		90 (53.3)
Current smoker		35 (20.7)
Former smoker		44 (26)
Presence of comorbidity, n (%)		108 (50.7)
Presence of pneumonia, n (%)		141 (66.2)
Respiratory failure, n (%)		32 (15)
Need for ICU, n (%)		5 (2.3)
Mortality, n (%)		6 (2.8)
Charlson Comorbidity Index		
Classical CCI	Median (25th-75th)	0 (0-1)
Classical CCI—age	Median (25th-75th)	1 (0-4)
Modified CCI	Median (25th-75th)	0 (0-1)
Modified CCI—age	Median (25th-75th)	1 (0-3.5)

BMI, body mass index; PCR, polymerase chain reaction; ICU, intensive care unit; CCI, Charlson Comorbidity Index.

elderly than younger ones. The ICU admission rate was also higher in older patients, but the difference was not statistically significant (5.3% vs. 1.3% $P = .09$).

Approximately 20% of the patients were obese (BMI ≥ 30 kg/m^2) in the study population. There was no significant difference in mortality rates between the obese and non-obese patients in this study. However, the rate of respiratory failure was significantly higher in obese patients ($P = .02$; odds ratio (OR): 3.1; 95% CI: 1.2-7.9).

Both median-modified and classical CCI scores and their age-adjusted scores were significantly higher in patients with pneumonia, respiratory failure, who required ICU, and who died (Tables 3 and 4). Furthermore, as the severity of comorbidity increased according to the classification of CCI, clinical outcomes such as pneumonia, respiratory failure, and mortality were increased. Clinical outcomes and mortality rates according to age-adjusted modified and classical CCI scores are shown in Figures 3 and 4.

Comparison of the patients according to the presence of pneumonia revealed that age ($P = .0001$), BMI ($P = .005$), and cigarette packs used in years ($P = .001$) were significantly higher in those with pneumonia. The rate of comorbidity was also higher in patients with pneumonia (65.2% vs. 22.2%, $P = .000$). Especially frequencies of HT, DM, COPD, and malignancy were found to be high in those with pneumonia, and these differences were statistically significant (Table 3). Coronavirus disease19 PCR test positivity was significantly lower in patients with pneumonia than cases without pneumonia (54.6% vs. 98.6%; $P = .000$).

Patients with respiratory failure were older ($P = .0001$), and they had higher comorbidity rates ($P = .000$). The presence of HT, DM, and malignancy was high in this group, and the differences were statistically significant (Table 3). The respiratory failure rate was significantly higher in patients with pneumonia ($P = .000$), and the presence of respiratory failure was significantly associated with mortality ($P = .000$).

Initial room air SO_2 was significantly lower in patients with pneumonia, respiratory failure, and mortality ($P = .0001$, $P = .0001$, $P = .03$, respectively).

Compared to the patients who died and survived, comorbidity was higher among those who died, but the difference was not significant (83.8% vs. 49.8%, $P = .12$). However, according to the subgroup analysis of comorbidities, CRD ($P = .04$) and malignancy ($P = .000$) were significantly higher in patients with mortality (Table 4).

DISCUSSION

Older age and comorbidities were found to be the risk factors for poor clinical outcomes in patients with COVID-19. There was a relationship between higher CCI scores and the rate of poor clinical outcomes and mortality.

In this study, there is a male predominance in COVID-19 patients.[14-17] In a meta-analysis, 53% of all COVID-19 cases were reported to be male.[14] In our study, 50.2% of the study population was male and there was no significant difference in gender distribution. Our study population was younger than reported in the previous studies and one-fifth of them were obese.[16,17]

Based on early data, it is estimated that in the USA and European Union, 80% of cases with COVID-19 result in mild illness, but 14% require hospitalization, and 6% require ICU admission.[18] Recently, it was shown that more than one-third of patients with COVID-19 were admitted to ICU globally.[19] In this study, the rate of the patients who were admitted to ICU was (2.3%) extremely lower than the literature.

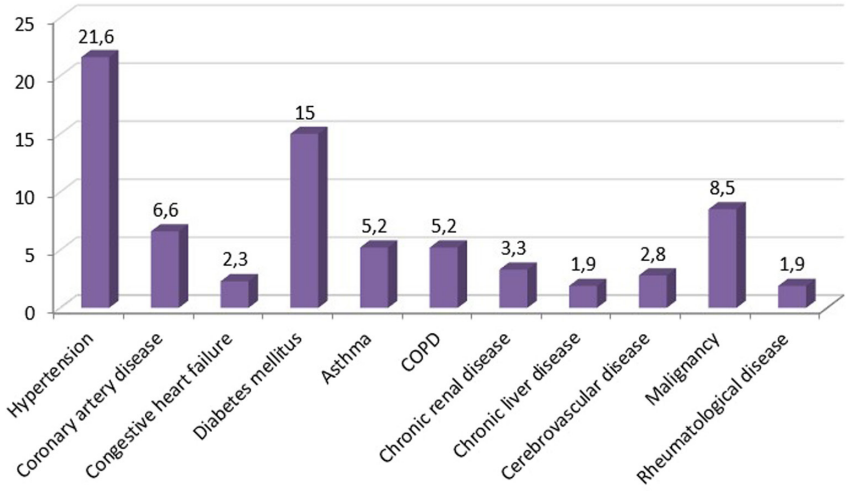


Figure 2. Most common comorbidities of the patients with COVID-19. COVID-19, coronavirus disease 19.

Table 3. Demographic and Clinical Characteristics and CCI Scores of the Patients According to the Presence of Pneumonia and Respiratory Failure

	Pneumonia (–)	Pneumonia (+)	*P*	Respiratory Failure (–)	Respiratory Failure (+)	*P*
Gender						
Women, %	55.6	46.8	.2	49.7	50	.9
Men, %	44.4	53.2		50.3	50	
Age, years, median	33.5	55	**.0001**	41	65	**.0001**
BMI, kg/m^2, median	24.6	26.9	**.005**	25.3	27.3	.95
Smoking pack of years, median	7.0	20.0	**.001**	11	30	**.002**
Comorbidity, %	22.2	65.2	**.000**	45.3	81.2	**.000**
HT	8.3	28.4	**.001**	18.8	37.5	**.02**
CAD	2.8	8.5	.1	7.7	0	.1
CHF	0.0	3.5	.1	1.7	6.2	.1
DM	2.8	21.3	**.000**	11.6	34.4	**.001**
Asthma	1.4	7.1	.08	4.4	9.4	.2
COPD	0.0	7.8	**.02**	5	6.2	.8
CRD	0.0	5	.06	2.8	6.2	.3
CLD	2.8	1.4	.5	2.2	0	.4
CVD	0.0	4.3	.08	2.2	6.2	.2
Malignancy	2.8	11.3	**.03**	5.5	25	**.000**
Modified CCI						
Median	0.0	0.0	**.001**	0.0	0.5	**.0001**
Modified CCI—age						
Median	0.0	2.0	**.0001**	0.0	3.5	**.0001**
Classical CCI						
Median	0.0	1.0	**.0001**	0.0	1.0	**.001**
Classical CCI—age						
Median	0.0	3.0	**.0001**	0.0	4.0	**.0001**

BMI, body mass index; HT, hypertension; CAD, coronary artery disease; CHF, chronic heart failure; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CLD, chronic liver disease; CRD, chronic renal disease; CVD, cerebrovascular disease; CCI, Charlson Comorbidity Index; SD, standard deviation.
P value <.05 was considered statistically significant.

Table 4. Demographic and Clinical Characteristics and CCI Scores of the Patients According to the Presence of ICU Stay and Mortality

	ICU (–)	ICU (+)	*P*	Mortality (–)	Mortality (+)	*P*
Gender						
Women, %	50.5	20	.2	49.8	50	.9
Men, %	49.5	80		50.2	50	
Age, years, median	46	67	.06	46	65	**.04**
BMI, kg/m^2, median	25.5	28.1	.6	25.4	26.6	.6
Smoking pack of years, median	15	30	.2	15	115	.053
Comorbidity, %	49.5	100	**.03**	49.8	83.3	.12
HT	21.6	20	.9	22.2	0	.2
CAD	6.7	0	.6	6.8	0	.5
CHF	2.4	0	.7	2.4	0	.7
DM	15.4	0	.3	15.5	0	.3
Asthma	4.8	20	.13	5.3	0	.6
COPD	4.3	40	**.000**	4.8	16.7	.2
CRD	3.4	0	.7	3.4	0	.7
CLD	1.9	0	.8	1.9	0	.7
CVD	2.9	0	.7	2.4	16.7	**.04**
Malignancy	7.2	60	**.000**	6.8	66.7	**.000**
Modified CCI						
Median	0.0	2.0	**.005**	0.0	2.5	**.007**
Modified CCI—age						
Median	1.0	4.0	**.01**	1.0	5.0	**.005**
Classical CCI						
Median	0.0	2.0	**.03**	0.0	2.5	**.005**
Classical CCI—age						
Median	1.0	4.0	**.02**	1.0	5.0	**.006**

BMI, body mass index; HT, hypertension; CAD, coronary artery disease; CHF, chronic heart failure; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CLD, chronic liver disease; CRD, chronic renal disease; CVD, cerebrovascular disease; CCI, Charlson Comorbidity Index; SD, standard deviation; ICU, intensive care unit.
P value <.05 was considered statistically significant.

Mortality data may vary by country and demographic features of the patients and range from 3.1% to 18%.[6,9,15-17] While the rate is as high as 15%-16% in the USA and Sweden,[15,16] it is 3.1% in China.[6] The mortality rate of our study was 2.8% In this study, the need for ICU and mortality rates were found to be lower than in the literature. These

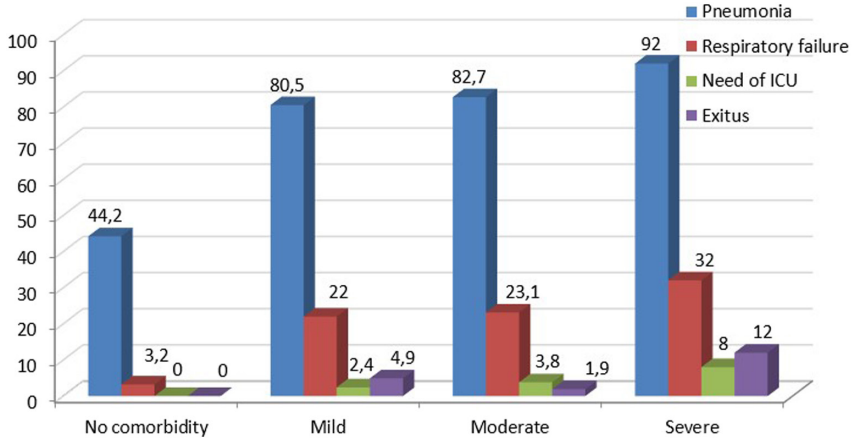


Figure 3. Clinical outcomes and mortality rates according to the classification of age-adjusted, modified CCI scores. CCI, Charlson Comorbidity Index.

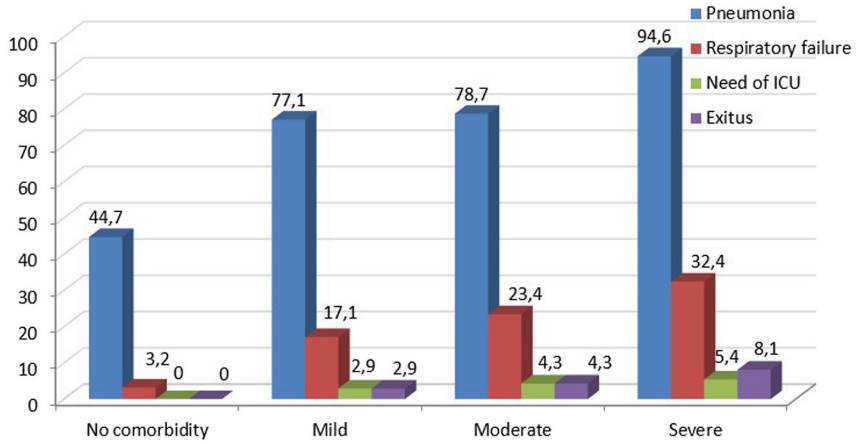


Figure 4. Clinical outcomes and mortality rates according to the classification of age-adjusted classical CCI scores. CCI, Charlson Comorbidity Index.

differences may be related to the heterogeneity of our study population, as it was younger and all patients were hospitalized and isolated in the early stages of the pandemic, regardless of disease severity.

There are multiple risk factors associated with mortality and severity of disease in COVID-19 patients. Studies had shown that age, male gender, and comorbidities are predictors of mortality.[15,19-23] Grasselli et al[20] reported that male gender was an independent risk factor of mortality.[20] Furthermore it was shown that there was an association between male gender and severity of the disease.[14,21] Age ≥ 65 years were associated with a higher risk of death during the hospital stay for COVID-19.[17] In contrast to these studies, poor clinical outcomes of the disease were similar between the genders in our study. However, older age was significantly a risk factor for pneumonia and respiratory failure.

The comorbidity rate of COVID-19 patients varies between 57.7% and 83%.[15,16,19,20,24] This broad range may be due to demographic differences of the study population, such as age. Also, it may differ depending on whether the study population includes all COVID-19 patients or only severe patients. In a review, among the 22 753 COVID-19 patients, 57.7% had one or more comorbidity.[24] There was a high rate of comorbidities (83%) at Pellaud et al's study.[16] The rate of comorbidity was 50.7% in our study. This rate, which is lower than the literature, may be related to the younger study population and not include intensive care patients.

Major comorbidities of COVID-19 patients are HT, DM, CVD, cancer, CRD, and COPD. Hypertension has the highest rate in all studies and its rate varies between 17% and 60%.[4,5,15-17,24,25] As similar to the literature, the most common comorbidities were HT, DM, and malignancy in our study.

Previous studies reported a correlation between the presence of comorbidity and mortality in patients with COVID-19.[4,5,19,21,26] The risk of death was increased in patients with DM, renal failure, and cardiovascular diseases such as heart failure and myocardial infarction.[4,5,26] The presence of comorbidity in COVID-19 was also related to severe disease and poor outcomes.[5,7,21] In a meta-analysis including 3994 COVID-19 patients reported that 13.16% of the patients had serious events (ICU admission, pneumonia, mechanical ventilation, ARDS, and death), and the presence of comorbidities increased the risk of developing serious events.[5] A systematic review revealed that comorbidities including HT, DM, cardiovascular disease, CVD, COPD, CRD, and malignancy had strong associations with the severity and prognosis of COVID-19.[21] Liang et al[25] reported that patients with cancer had a higher risk of COVID-19 with a poorer prognosis than those without cancer.[25]

In this study, pneumonia, respiratory failure, and ICU admission rates were significantly higher in patients with comorbid diseases than patients without any comorbidity. The rate of HT and DM was significantly higher in patients with pneumonia and respiratory failure. Chronic obstructive pulmonary disease rate was significantly higher in patients with pneumonia and who needed to stay in ICU. Comparison of the patients according to mortality revealed that the presence of comorbidity was higher among those who died, but the difference was not significant (83.8% vs. 49.8%, P = .12). However, according to the subgroup analysis of comorbidities, CRD (P = .04) and malignancy (P = .000) were significantly higher in patients with mortality.

Charlson Comorbidity Index is a tool for calculating comorbidity scores using a predefined list of medical conditions and also it can be adjusted for age. It is an easy-to-perform and validated index estimating the risk of mortality related to comorbid disease and has been studied in many diseases.[8,11-13] Coronavirus disease 19 is also one of these diseases, and studies evaluating the effect of CCI on mortality in COVID-19 patients have been increased in the literature.[9,27-29] A recent systematic review and meta-analysis revealed that a higher CCI score was associated with increased mortality and severity of the disease in patients with COVID-19. There was a 16% increase in mortality for each increase in CCI score.[28] The CCI score >3 (OR: 2.71; 95% CI: 1.85-3.97) was found to be associated with mortality.[15] Gregoriano et al[30] reported that patients had a high burden of comorbidities, with a median CCI of 3 points.[30] It is found that CCI score above 0 was associated with an increased risk of severe COVID-19 and death when controlled for age and sex.[9] There was also an increasing trend in the length of stay in the hospital related to increasing CCI scores.[29]

In some studies, categorized CCI score[9,27] was used, while in others, both the median CCI score and the categorized CCI were evaluated together.[28,29] In our study, both median scores and categorized CCI were evaluated to improve the power of the study. The median scores of CCI and age-adjusted CCI were 0.00 and 1.00, respectively, in all study populations. These scores were relatively lower than the literature, but it is thought that it might be explained by the younger study population. Despite the relatively low CCI score in all patients with COVID-19, both median-modified and classical CCI scores and their age-adjusted scores were significantly higher in patients with poor clinical outcomes including pneumonia, respiratory failure, the need for a stay in ICU, and mortality. In addition, it was observed that as the severity of comorbidity increased according to the classification of CCI scores, poor clinical outcomes were also increased. These results were similar to the literature.

Modified CCI is a shorter and simpler form of CCI.[13] Unlike CCI, comorbidities do not include myocardial infarction, peripheral vascular disease, CVD, peptic ulcer, and uncomplicated diabetes. However, thromboembolic complications are frequent in patients with COVID-19. In addition, DM is one of the most common comorbidities. In order not to ignore the effect of these comorbidities, both classical CCI and modified CCI were evaluated in our study. However, the effects of both classical and modified CCI scores on poor clinical course and mortality were similar.

There are some limitations of this study. At first, it was a retrospective study and it was carried out in a single center (a university hospital). Second, the study population included a limited number of patients, with a median age of 46 years. Approximately one-quarter of the population is 65 years old or older. Especially, the relatively small number of the elderly population, where comorbidities are common, may not reflect the real effect of the severity of comorbidity. Third, retrospective screening of comorbidities from the database and calculating CCI seems problematic. However, since the first day of the pandemic in our clinic, medical information and comorbidities of inpatients have been recorded in detail in order to reduce unknowns about COVID-19. Therefore, we believe that this issue can be ignored.

In conclusion, older age and comorbidities were associated with poor clinical outcomes in patients with COVID-19. Charlson Comorbidity Index was significantly higher in patients with poor clinical outcomes including pneumonia, respiratory failure, intensive care, and death. There was a relationship between higher CCI scores and the rate of poor clinical outcomes and mortality. It is thought that evaluating the CCI score during the initial admission will contribute to the identification of the risky group and the preparation of an early action plan.

Ethics Committee Approval: This study was approved by Ethics committee of Kocaeli University, (Approval No: GOKAEK-2020/11.19).

Informed Consent: As informed consent from patients to review their medical records was not obtained, patient data were de-identified.

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Author Contributions: Concept – S.A.B., H.B., S.A., B.M., M.D., İ.B.; Design – S.A.B., H.B., S.A., B.M., M.D., İ.B.; Supervision – S.A.B., H.B., M.D., İ.B.; Resources – S.A.B., H.B., İ.B.; Materials – S.A.B., H.B., S.A., B.M., M.D., İ.B.; Data Collection and/or Processing – S.A.B., M.D., İ.B.; ; Analysis and/or Interpretation – S.A.B., M.D., İ.B.; Literature Search – S.A.B., M.D.; Writing Manuscript – S.A.B., M.D., İ.B.; Critical Review – S.A.B., H.B., İ.B.

Declaration of Interests: The authors have no conflict of interest to declare.

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Review

Pulmonary Rehabilitation in Coronavirus Disease 2019 Patients

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Abstract

Since coronavirus disease 2019 mainly affects the respiratory system, pulmonary rehabilitation has increased its importance during the novel coronavirus pandemic. Healthcare professionals must use appropriate personal protective equipment during rehabilitation of patients infected with severe acute respiratory syndrome coronavirus 2. Comorbidities of the patient should be taken into consideration while organizing the rehabilitation program. Clinical manifestations range from asymptomatic to acute respiratory distress syndrome. There is no need for pulmonary rehabilitation in asymptomatic patients. Pulmonary rehabilitation may be recommended in patients with mild-moderate disease. It is advised that patients be followed up during the rehabilitation period. Positioning and passive range of motion exercises are beneficial in preventing immobilization complications in patients with critical illness. Post-coronavirus disease 2019 rehabilitation program should be established according to the needs and functional levels of the patients.

KEYWORDS: Pulmonary rehabilitation, COVID-19, SARS-CoV-2
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INTRODUCTION

Since the beginning of the pandemic, more than 96 million people worldwide have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19). More than 2 million people have been recorded killed by the virus since the disease first emerged in China.[1]

Pulmonary rehabilitation (PR), as defined by the American Thoracic Society (ATS) and the European Respiratory Society (ERS), is an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often with limitation in activities of daily living. Individualized pulmonary rehabilitation programs provided to the patient in conjunction with medical treatment are designed to reduce symptoms, optimize functional status, increase participation, and reduce healthcare costs by stabilizing or reversing the systemic symptoms of the disease.[2] To minimize the negative effects of COVID-19, the World Health Organization also recommends rehabilitation practices in these patients.[3]

Post-COVID-19 rehabilitation programs can be diverse and comprehensive. Rehabilitation programs are organized to prevent immobilization complications and secondary musculoskeletal problems and to increase respiratory functions, patient independence, and quality of life, taking the patient's comorbidities into account. The purpose of PR after COVID-19 is to decrease dyspnea, relieve anxiety, reduce complications, minimize disability, preserve function, and improve quality of life.[4]

In this review, pulmonary rehabilitation practices and their efficacy after COVID-19 will be discussed with the current literature.

CLINICAL AND RESEARCH CONSEQUENCES

General Principles

Since transmission risk is high during the acute phase of COVID-19, PR applications should be performed with minimal contact. Telerehabilitation is a safe and cost-effective method mainly used in the treatment of disability caused by different neurological diseases such as stroke, spinal cord injury, and multiple sclerosis.[5] Also, it has been shown to be an effective and safe treatment method in the rehabilitation of different respiratory tract diseases such as chronic obstructive pulmonary disease (COPD), asthma, and cystic fibrosis.[2,6] In addition to treatment with telemedicine methods, functional status of the patients can also be evaluated. The Hull University-proposed pathway recommends that all COVID-19 survivors should be evaluated in terms of rehabilitation needs. Monitoring of symptoms and radiological follow-up, and evaluation by a multidisciplinary team 6-12 weeks after discharge were recommended.[7] In telerehabilitation applications, patients should be evaluated with a multidisciplinary team within the framework of the International Classification of Functioning, Disability, and Health.

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In a case series that implemented a telehealth COVID-19 rehabilitation model, it has been concluded that rehabilitation via telehealth for individuals recovering from COVID-19 was safe and feasible. With telemedicine and videoconference methods, it is possible to evaluate patients, prescribe individualized exercise methods, and monitor patients through appropriate equipment during exercise.[8] However, patients with limited cooperation, comorbidities, communication problems, and complex symptoms require detailed evaluation, thus telemedicine methods may not be suitable for these patients.

If the patient infected with SARS-CoV-2 is not suitable for telemedicine and the PR program needs to be implemented directly, it is critical that the healthcare professional use appropriate personal protective equipment (PPE). It is recommended that the rehabilitation professional use full PPE including gloves, masks, and isolation gowns for all person-to-person interactions. Also, a face shield and/or goggles are recommended if there is a risk of airborne transmission.[9] Recommendations for rehabilitation centers to prevent the spread of the disease are given in Table 1.

Table 1. Recommendations for Rehabilitation Centers

All healthcare workers should use appropriate PPE.
Surgical mask, eye protection, gloves, and disposable gown should be worn during aerosol-generating procedures.
Patients should use a surgical mask during rehabilitation practices.
It is recommended to use negative pressure systems and HEPA filters in exercise rooms.
There should be at least 30 minutes between patients to be evaluated in the exercise test room.
Surfaces should be sanitized after each patient's rehabilitation session.
The number of patients to be rehabilitated at the same time should be determined according to the size of the area.
Patient appointments and waiting room should be arranged to provide social distance.

PPE, personal protective equipment; HEPA, high-efficiency particulate air.

The main goals of PR are to prevent secretion accumulation with appropriate methods (such as positioning, mobilization, cough, and postural drainage) and to reduce respiratory tract resistance, ensure that respiratory muscles are in proper position and function, reduce energy consumption during breathing, increase chest mobility, correct postural deformities, reduce dyspnea, increase general exercise tolerance, decrease depression and anxiety, and to increase functionality and quality of life.[10]

The international task force coordinated by the ERS and ATS recommends bedside (critical care and/or ward-based) PR for hospitalized patients with COVID-19. It was also recommended that, similar to the case with other critical illnesses, at the onset of PR, the patient discharged from the hospital be evaluated in terms of compliance. However, it was stated that some specialists in the task force had some concerns about patient safety due to the possible impact of rehabilitative interventions since the understanding of the pathophysiology is limited and it is still unknown if there is any threshold of disease severity.[11] There is not yet a core set for baseline assessment of patients.[12]

MAIN POINTS

- Healthcare professionals are required to use appropriate personal protective equipment.
- Pulmonary rehabilitation (PR) programs can be presented with telerehabilitation methods in eligible patients.
- There is no need for PR in asymptomatic patients.
- Comorbidities and functional status of the patients should be taken into consideration while organizing the PR program.
- Pulmonary rehabilitation is recommended after patient evaluation in COVID-19 pneumonia.
- Individualized programs are recommended in PR.
- It is recommended to reduce the adverse effects of immobilization and secretion during acute respiratory distress syndrome.
- High-quality studies are needed for post-COVID-19 exercise recommendations.

Differences in the duration of COVID-19 symptoms also create different opinions in the timing of PR. Around 35% of patients with polymerase chain reaction (PCR) (+) stated that they could not return to their normal health status even 3 weeks after diagnosis. In the evaluation made 14-21 days after the diagnosis of COVID-19, it was stated that 20% of patients aged 18-34 could not return to usual health. This rate was found to be 47% in patients older than 50 years.[13] In another study including 143 patients, only 12.6% of individuals who were followed up for an average of 60 days after the diagnosis of COVID-19 reported no symptoms, 32% had 1-2 symptoms, 55% had 3 or more symptoms, 44.1% reported worsening in quality of life, 53.1% reported fatigue, 43.4% reported shortness of breath, 27.3% reported joint pain, and 21.7% reported chest pain.[14] With this information, it can be said that SARS-CoV-2 can cause symptoms that may continue for a long time after the disease. This situation should not be forgotten while considering patient education and PR timing. In addition to the publications suggesting that patients should start PR early after COVID-19, there are also publications suggesting that patients should be evaluated 6-8 weeks after discharge.[15] There is currently no generally accepted recommendation regarding the timing of PR.

Patient education plays an important role in achieving rehabilitation success. Patient education can be applied via video conferencing, information booklets, telephone calls, and video calls. Patients should be educated about the clinical course of COVID-19 and their own comorbidities, if any.[16] Recommendations for the management of additional conditions such as smoking, overweight, inadequate fluid intake, and poor sleep hygiene should be offered to patients infected with SARS-CoV-2.[10] It is recommended to advise and educate patients on fatigue, dyspnea, mood disorders, and social isolation in the early period after discharge.[15]

Emotional state of the patients is an important factor in the success of rehabilitation in many diseases that cause disabilities, including COVID-19. Cognitive impairment, post-traumatic stress disorder, anxiety disorder, chronic pain, sleep disturbance, fatigue, and fibromyalgia have been shown in patients after COVID-19. It is stated that these emotional changes may be caused by a prolonged stay in an intensive care unit (ICU), immobilization, social isolation, disruption of the sleep–wake cycle, as well as general inflammation or neurotropism of SARS-CoV-2.[17] Therefore, patients should be evaluated in terms of emotional functionality within 6-8 weeks after discharge in order to determine their rehabilitation needs.

Pulmonary Rehabilitation Recommendations According to the Stage of the Disease

a report of 72 314 cases from the Chinese center for disease control and prevention, 81% of the patients were classified as mild (without or with mild pneumonia), 14% as severe (dyspnea, blood oxygen saturation <93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, or lung infiltrates >50% within 24-48 hours), and 5% as critical disease (acute respiratory distress syndrome (ARDS), septic shock, or multiple organ dysfunction).[18]

The recommendations made by Zhao et al[4] for PR after COVID-19 are as follows: (1) PR can be used to reduce dyspnea, anxiety, and depression, and improve physical function and quality of life; (2) early respiratory rehabilitation is not recommended for severely/critically ill patients; (3) PR programs for patients should be implemented through training videos, informational documents, or telerehabilitation; (4) patients should be evaluated and monitored during PR; and (5) in case of face-to-face contact, appropriate PPE should be used.

1. Acute Phase Management

a. Asymptomatic Disease Management

There is no need for PR application in asymptomatic patients. Low-to-medium intensity stepping and range of motion exercises can be recommended to protect patients from the negative effects of immobilization during the quarantine period.[10]

b. Mild Disease Management

No signs of pneumonia on imaging and mild symptoms are considered to be mild illness in COVID-19. In mild disease, PR can be applied in an outpatient setting using the telehealth technique.[19] Pulmonary rehabilitation program in mild disease includes patient education, activity guidance, breathing exercises, airway clearance techniques, anxiety management, and physical exercise.[4] A home-based rehabilitation program can be recommended for patients with mild illness and no additional risk factors. The main goal of rehabilitation in this patient group is to avoid inactivity complications.[19] The criteria for patient stabilization after COVID-19 infection include decreased fever, decreased dyspnea, respiratory rate <30 breaths/min, and SpO_2 >90%. In the period when virulence decreases, individualized PR program can be performed for suitable patients. In patients with mild pneumonia, range of motion exercises (active-assisted or active), mobilization exercises, general muscle strengthening exercises, and bronchial hygiene techniques (use of incentive spirometry or triflow, controlled cough, and huffing maneuver) can be given in the PR program. It is not necessary to use airway cleaning techniques in patients having dry cough and no sputum.[10]

Patients who do not have additional risk factors after mild COVID-19 should have warm-up, exercise, and cool-down periods. During warm-up and cool-down, there should be at least 5-10 minutes of low-intensity endurance exercises. Aerobic exercises and resistance training can be recommended in the exercise program. Aerobic exercises should be done >5 days a week, 30-60 minutes per session, and targeting 40-59% of heart rate reserve. Resistance exercises should aim at strengthening large muscles such as biceps, triceps, deltoid, pectoralis major, gluteus, iliopsoas, quadriceps, hamstring, anterior tibialis, and calf muscles. Strengthening exercises can be recommended 2-3 days a week (with appropriate rest intervals) using weight 60-70% of the 1 repetition maximum, 2-3 sets, and each set with 8-12 repetitions. For endurance training, the number of sets can be decreased (1-2 sets) and the number of repetitions can be increased (15-25 repetitions). Exercise recommendations for mild COVID-19 patients with comorbidities should be disease-specific. In patients with hypertension, blood pressure should be monitored during exercise, sufficient cooling exercise should be recommended for heart rate and blood pressure to return to normal, and movements such as the Valsalva maneuver that increase blood pressure should be avoided. Exercise should be stopped if patients with cardiovascular disease have symptoms of exercise intolerance such as shortness of breath, palpitations, chest pain, and dizziness. Because of the QT prolonging effect of drugs used in the treatment of COVID-19, a cardiology consultation may be requested for exercise safety. In patients with diabetes mellitus, blood glucose should be controlled before and after exercise. Patients should be followed closely for signs of hypoglycemia (tremor, abnormal sweating, confusion, visual impairment, etc.).[19]

Breathing exercises can be performed in COVID-19 patients with mild involvement. The purpose of diaphragmatic breathing is for the patient to learn how to use the diaphragm, which is the main muscle of inspiration while breathing, and thus to minimize the movement of the auxiliary respiratory muscles. In diaphragmatic breathing, the first breathing is through the nose and the abdomen is inflated, and then the mouth is opened and the breath is exhaled. In a randomized controlled trial (RCT) investigating the effectiveness of PR after COVID-19 in elderly patients, respiratory muscle training, coughing, diaphragmatic breathing, and stretching exercises were applied 2 days a week for 6 weeks. Significant increases were detected in the respiratory functions, functional capacity, and quality of life of the patients in the intervention group at the end of 6 weeks.[20] The practices used in respiratory physiotherapy including incentive spirometry, respiratory muscle training, diaphragmatic breathing, pursed-lip breathing, and bronchial hygiene techniques are not recommended in patients with COVID-19 during the acute phase in order not to cause an additional burden on the work of breathing.[21]

c. Moderate/Severe Disease Management

Symptomatic patients with respiratory distress, respiratory rate >30/min, resting oxygen saturation <93%, or PaO_2/FiO_2

<300 mmHg are considered as having moderate/severe illness. Hospitalization and monitoring of these patients are recommended.[4] Although there is insufficient evidence for PR applications in the acute phase of COVID-19, the efficacy and safety of PR in COPD exacerbations have been studied previously. It has been reported that PR programs increased the exercise capacity and health-related quality of life of patients with COPD exacerbations, and no significant side effects were observed.[22] In addition, there are studies indicating that early rehabilitation programs after interstitial pneumonia reduce mortality.[23] In early PR and mobilization practices, besides evaluation of patients, it is important to evaluate the hospital conditions and the safety of healthcare workers. During PR and mobilization, SARS-CoV-2 aerosols may spread into the environment, so proper PPE use is essential for the protection of healthcare workers and other patients.[24]

Due to the risk of disease progression and serious disease development in a short time after being infected with SARS-CoV-2,[25] the exercise intensity should be carefully evaluated in the PR program and appropriate patients should be monitored. The criteria for the patients not to be included in the PR program during the acute disease period are as follows: (1) body temperature >38.0°C; (2) if the time to first diagnosis or onset of symptoms is 3 days; (3) if the time interval between disease onset and dyspnea is ≤3 days; (4) chest image showing >50% progression within 24-48 hours; (5) SpO_2 <90%; (6) blood pressure <90/60 mmHg or >180/90 mmHg; (7) respiratory rate >40/min; (8) heart rate <40/min or >120/min; (9) the presence of new-onset arrhythmia and myocardial ischemia; and (10) altered level of consciousness.[4,26]

Physical exercise is the main point of the PR program, but in immobile patients, the PR program can be started with passive or active in-bed exercises.[2] During PR, saturation should be maintained at >90%. In order to achieve this goal, oxygen support should be used if necessary. Exercise should be interrupted if the saturation value falls below 90% or if the modified Borg dyspnea scale score is >3.[26] Exercise practices should also be stopped in the presence of palpitations, chest pain, and dizziness.[2]

d. Critical Disease

Critical illness includes ARDS, sepsis, and septic shock. Radiological and clinical worsening is seen in patients with ARDS. The patient's symptoms cannot be explained by cardiac functions and fluid overload. Although there are publications reporting that lung volumes and spirometric measurements were normal by 6 months after ARDS,[27] there are also publications reporting obstructive involvement in 6-43% of patients and restrictive effects in 15-58% of patients on pulmonary function test performed within the first year after ARDS.[28] There is insufficient evidence on the effect of early mobilization of critically ill patients in ICU on physical function, muscle strength, performance, adverse events, and health-related quality of life.[29]

Evidence of septic shock hypotension (systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or vasopressor requirement), clinically significant acute renal, hepatic, or neurological dysfunction have been reported in COVID-19-infected patients.[30] Pulmonary rehabilitation application is not recommended during these periods when the patient is not stable. Patients who survive severe disease should be evaluated individually and a PR program should be organized after their viral load decreases. Pulmonary rehabilitation application should be stopped in case of progression of the disease, presence of respiratory rate >30 breaths/min, increased respiratory workload and dyspnea, SpO_2 <90% under oxygen therapy or more than 4% decrease from baseline value, fever, chest pain, dizziness, severe headache, symptoms such as visual impairment, imbalance, tinnitus, palpitations, excessive sweating, and radiological lesion progressing more than 50% within 24-48 hours. Positioning, passive range of motion (ROM) exercises, and procedures for secretion management can be applied to the patient in the ARDS period. In positioning, the patient should stay in the prone position for 12-16 hours a day. The position of catheters should be checked during transitions between the supine and prone positions and the safety of the patient should be ensured. Immobile patients should be checked regularly for pressure ulcers. In order to prevent joint contracture, the patient should be applied a joint ROM exercises (passive/active-assisted/active depending on the patient's condition) at least once a day for 15 repetitions.[10]

2. Post-Acute Phase Management

In the staging of COVID-19, in the early infection stage (stage 1), symptoms such as fever, diarrhea, and cough are seen; dyspnea, hypoxia, and pulmonary involvement are observed in the pulmonary phase (stage 2); and in the hyper inflammation phase (stage 3), ARDS, shock, multiple organ failure, and death are the undesired outcomes.[31] Since the long-term effects of the disease are not fully known, post-COVID-19 PR recommendations are generally based on studies in other respiratory diseases and expert opinion.

After the acute phase of the disease, during the recovery period, early rehabilitation applications are recommended. According to the needs of the patient, neuromotor rehabilitation may be done in a rehabilitation center or at home. Patients and healthcare professionals should use appropriate PPE at all treatment stages. The oxygen level of the patients should be monitored closely and at least 90% peripheral oxygen saturation should be provided. Adequate support should be provided in terms of psychological advice and counseling in the post-COVID-19 period. The intervention should be stopped in the presence of symptoms such as high fever, increased shortness of breath, tachypnea (>30 breaths per minute), decreased peripheral oxygen saturation during exercise (>4%), and respiratory distress. Posture changes and management, including prone, sitting, or semi-orthopneic positions, can be done to increase systemic oxygenation in COVID-19 patients with FiO_2 ≥40 and <60%. In the post-acute period, ROM exercises, stretching exercises, and ankle pumping exercises can be applied to immobile patients. Thrombosis after COVID-19 is common; performing these exercises is important for preventing conditions such as deep vein thrombosis and pulmonary embolism. The following can be applied to patients in the PR program: controlled breathing, chest–abdominal coordination exercises, and clearance techniques.[32]

While the oxygen requirements of patients generally decrease, the oxygen need of some patients continues after discharge.[33] Some patients may experience dyspnea and oxygen desaturation during exercise that are not observed at rest. For this reason, it is recommended to evaluate the oxygen requirement of patients at rest and during effort before discharge.[11] As the lung pathology improves, the oxygen need of the patients may decrease, so follow-up planning should be done to evaluate the oxygen need after discharge. Patients with low oxygen needs (FiO_2 ≥21 and <40) have better functional capacity, and active ROM exercises and muscle strengthening exercises can be given to these patients as a part of the PR program. It is important to improve mobilization and balance in the post-acute period. Fatigue and dyspnea levels should be monitored and exercises should be started at low intensity. Walking training should be initiated in patients who can stand and have appropriate muscle strength. Thoracic expansion training, forced inspiration/expiration, intensive spirometry, and positive expiratory pressure can be used to improve pulmonary function in COVID-19 patients with FiO_2 ≥21% and <40%.[32]

In a study where an individualized cardiopulmonary rehabilitation program (aerobic exercise and strengthening exercises) was applied to patients after COVID-19, significant increases were found in the 6-minute walking test in both mechanically ventilated and not ventilated groups.[34] There is insufficient evidence for the use of aerobic exercises such as treadmills and cycle ergometers after COVID-19.

Some of the patients have difficulty during daily activities after COVID-19. Patients with long-term hospitalization, serious illness, comorbidities, and persistent symptoms may have difficulty during daily activities.[11] It has been shown that most of the patients who developed acute respiratory failure due to different diseases had significant increases in their physical functions in the second month after discharge. Advanced age, prolonged sedation time, and longer length of stay at ICU are factors that negatively affect functional recovery.[35] It is important to encourage patients to do daily activities within 6-8 weeks after discharge in order to increase their physical functions. However, patient's oxygen saturation, perceived difficulty, and dyspnea should be evaluated regularly.[11]

Prescribing exercise after COVID-19 is a delicate issue. Oxygen desaturation may occur with exercise due to the ongoing inflammatory process and persistent symptoms in discharged patients. It is stated that moderate-intensity exercises are safe and feasible in critical illness survivors.[36] In an RCT evaluating the effectiveness of exercise after SARS, patients in the exercise group had significant improvement in pulmonary function, muscle strength, and 6-minute walk distance.[37]

There are no detailed studies on the effects and prescription of exercise after COVID-19. Some clinicians suggest that there is no need for exercise restriction in asymptomatic patients following mild illness.[38] During the mild illness period, a low-medium intensity exercise program can be given in accordance with the patient's symptoms, comorbidities, and physical capacity. Some clinicians also want to be more cautious about prescribing exercise due to the possibility of long-term disease, especially cardiovascular complications.[39]

Although it has been shown that regular exercise has positive effects and is a safe method in chronic fatigue syndrome,[40] it is not clear whether exercise has an effect on fatigue after COVID-19. It is known that peripheral muscle dysfunction develops in patients with ARDS and those requiring prolonged ICU stay. Peripheral muscle weakness is associated with immobilization, inflammation, myopathy, neuropathy, and medication. Peripheral muscle strengthening is an important part of PR in suitable patients with chronic respiratory disease. Although there is insufficient evidence for the benefits of lower extremity muscle strengthening after COVID-19, it is recommended that patients with lower extremity weakness or dysfunction begin a strengthening program 6-8 weeks after discharge.[2] The muscle strengthening program should be appropriate for the functional level of the patient, applicable, and progressive.

Proper protein and calorie intake is required for the patient to regain functional muscle mass or to minimize muscle loss. Coronavirus disease 2019 patients may experience appetite problems, loss of taste and smell, and swallowing disorders.[41] Appropriate nutritional supplements and moderate-intensity physical exercises at home are recommended for COVID-19 survivors after discharge.[11]

It should be kept in mind that COVID-19 survivors may be at different functional levels; hence, individualized rehabilitation programs should be created. It is recommended to perform re-evaluation every 3 months for 1 year after severe illness. Follow-up after critical/serious illness should be performed by a multidisciplinary team, taking extrapulmonary involvement into consideration.[12]

Physical examination, laboratory tests, and imaging methods can be used in the clinical evaluation of COVID-19 survivors. To evaluate respiratory functions, respiratory muscle strength assessment and respiratory function test can be done. A manual muscle test, UK Medical Research Council Scale or isokinetic muscle test, and goniometric ROM measurement can be used to evaluate exercise capacity. Berg balance scale to evaluate balance functions; 6-minute walking test and cardiopulmonary exercise test to evaluate aerobic exercise capacity; Physical Activity Scale for Elderly and International Physical Activity Questionnaire for physical activity assessment; and the Barthel index to evaluate activities of daily living can be administered.[4] However, respiratory function test and cardiopulmonary exercise test are not recommended in the acute phase of the disease due to the risk of contamination.[42] Although exercise capacity can be evaluated remotely and practically with sit-to-stand and timed up-and-go tests, exercises should not be prescribed to patients based on these tests.[43]

In addition, scores of symptom scales, infectious disease/immunological status, hematological data, imaging results, cardiorespiratory function, nutritional status, and comorbidities should be evaluated regularly. It is necessary to monitor the gas exchange during the PR process. Although arterial blood gas measurement (PaO_2/FiO_2) is the gold standard for evaluation, it is recommended that all patients use pulse

oximetry during exercise at home. Evaluation of frailty is important to predict the course and effectiveness of PR. In frailty measurements, patients should be evaluated for exercise capacity, muscle strength, balance, coordination, nutrition, and psychosocial status multidimensionally.[12]

3. Chronic Phase/Complications Management

Comorbidities detected in COVID-19 patients are as follows: hypertension (55%), coronary artery disease and stroke (32%), diabetes mellitus (31%), COPD (7%), malignancy (6%), chronic renal failure (4%), gastrointestinal diseases (3%), and immunodeficiency (1%).[44] In the rehabilitation program to be implemented after COVID-19, additional diseases and functional status of the patient should be considered.

Critical disease polyneuropathy (CIP) is a sensorimotor neuropathy with axonal degeneration. It can be seen in up to 46% of patients hospitalized in the ICU with a diagnosis of ARDS. Clinical signs of CIP are atrophy, distal sensory loss, symmetrical weakness (respiration may be negatively affected by diaphragm involvement), and decrease or absence of deep tendon reflexes. As a result of CIP, ROM limitation, pain, incontinence, gait disturbance, loss of balance, and dysphagia can be observed.[45] There is no precise data on the prevalence of CIP after COVID-19.

Critical disease myopathy (CIM) is present in 48-96% of patients hospitalized in the ICU with a diagnosis of ARDS. Myopathy may be associated with corticosteroids, inflammation, and paralysis. Weakness, decreased endurance, decreased quality of life, and loss of function can be seen in patients with CIM.[46] As with CIP, there is no scientific evidence yet for CIM prevalence among COVID-19 survivors.

It has been shown that 20% of COVID-19 patients have a cardiac injury. The incidence of mechanical ventilation need and death has been reported to be higher in patients with cardiac injury. It has also been stated that ARDS, acute kidney damage, electrolyte disturbance, and coagulation disorders were more common in patients with cardiac injury. Persistent tachycardia or new-onset or worsening hypertension may occur in patients with cardiac damage after COVID-19. The mechanism of COVID-19 cardiac injury is unclear. According to the hypothesis, the high affinity of the spike protein of SARS-CoV-2 to the angiotensin-converting enzyme-2 receptor may be associated with cardiac injury. It has been reported that cardiac involvement of SARS-CoV-2 may cause acute myocarditis, myocardial edema, and acute myocardial damage.[47]

Neurological involvement has also been reported in patients with COVID-19. Encephalitis, aortic ischemic stroke, cerebral edema, and headache are some of the neurological involvements. In addition, lymphocyte and monocyte infiltration in the vessel wall, ischemic changes of neurons, and demyelination of nerve fiber have also been reported. It has been stated that there may be an increased risk of stroke after infection as a result of hypoxia and vascular changes.[48]

Heterotopic ossification, adhesive capsulitis, decubitus ulcer, contracture, and osteoporosis can be seen as immobilization complications in COVID-19 patients requiring mechanical ventilation. Brachial plexus injury and peripheral nerve entrapment may be observed due to positioning and muscle imbalance.[49]

In a study evaluating the impact of COVID-19 on cognitive functions, it was found that patients with severe respiratory symptoms and long-term hospital stay were negatively affected. Decrease in cognitive functions may have a negative effect on rehabilitation success.[50]

CONCLUSION

The COVID-19 pandemic continues to affect the whole world. With the increase in scientific data and a better understanding of the disease, post-COVID-19 rehabilitation practices have also gained importance. Further randomized controlled studies are needed to evaluate the effectiveness of post-COVID-19 rehabilitation programs. With telerehabilitation applications, it is possible to reach a wide audience and make a great impact.

Physical medicine and rehabilitation physicians can play an important role in increasing patients' functionality and reducing disability during the SARS-CoV-2 outbreak. Although scientific evidence is not sufficient for PR after COVID-19, recommendations can be made considering the effectiveness of PR programs in different lung diseases.

Proper patient selection and protection of healthcare professionals are priorities in a PR program. Physical medicine and rehabilitation doctors can provide guidance about nutrition, airway clearance techniques, posture, breathing exercises, stretching, strengthening, and physical activity for patients recovering from COVID-19.

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Review

Turkish Thoracic Society Early Career Members Task Force Group's Virtual Congress Notes: European Respiratory Society International Congress 2020

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Abstract

In this article, Early Career Task Force Group members of the Turkish Thoracic Society summarize the European Respiratory Society 2020 virtual congress. Current developments in the field of respiratory diseases were compiled with the addition of sessions specific to coronavirus disease 2019 this year. Almost all of the congress sessions were examined, and the important and striking results of the congress were highlighted. Congress sessions were attended by expert researchers, and the prominent messages of each session were highlighted in short summaries. They were then grouped under relevant titles and ranked in order of meaning and relation. It was finalized by a team of researchers.

KEYWORDS: Respiratory diseases, Lung health, European Respiratory Society, congress highlights
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INTRODUCTION

The European Respiratory Society (ERS) International Congress was held virtually in 2020 due to the coronavirus disease 2019 (COVID-19) pandemic that seriously affected the world. The congress brought together respiratory researchers with exciting, leading, and current issues although it could not be held with individual participation. Current research and developments on respiratory system diseases and also special sessions for COVID-19 were conveyed in the congress.

Congress sessions were closely followed by the members of the Turkish Thoracic Society (TTS). Turkish Thoracic Society Early Career Members Task Force Group (TTS-ECMTG) members also attended most of the congress sessions while struggling with the pandemic in their institutions. As a product, an electronic booklet containing ERS session summaries was published after the congress.[1] In this way, researchers and physicians who could not attend the congress due to the pandemic were able to access up-to-date information more easily.

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A collective and systematic path was followed in the preparation of this article. Fifty-three sessions that stood out at the ERS 2020 congress were carefully selected. The sessions were apportioned and attended by the authors mentioned in the article, and highlights of each session were compiled. The notes of the sessions were combined under headings according to the subjects and turned into an article.

There are the efforts and perspectives of the real heroes fighting the pandemic in this article which compiles the current data provided by the ERS International Congress 2020 with the perspective of the TTS-ECMTG. This article is planned in order to present up-to-date data in aggregate, highlight important messages, and also to guide scientific meetings and research to be conducted in the upcoming years.

CORONAVIRUS DISEASE 2019

In the presentations about the recapitulation of COVID-19, it was pointed out that it is a pandemic with over 84 million cases worldwide, causing over 1 million deaths.[2] Although severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first seen in Wuhan, China's Hubei province in early December 2019, the disease is thought to have emerged around October 2019.[3]

Basic science point of view revealed that SARS-CoV-2 is one of the sub-types of viruses belonging to the β-coronavirus genus. Judging by the structure of the virus, it contains a single-stranded RNA genome and is protected by the nucleocapsid protein. In addition to being surrounded by lipid membrane and envelope proteins, it contains spike proteins (formed in the S1 and S2 domains) on its surface. The virus binds to the angiotensin-converting enzyme 2 (ACE2) receptor of the host cell with the S1 domains located on the upper part of the spike proteins.[4,5] It was also reported that peripheral blood mononuclear cell analysis is important for the characteristic of the disease. As a result of the studies, it was reported that the neutrophil/T-cell ratio is a better predictor than the neutrophil/lymphocyte ratio. Spike protein can enter broncho-epithelial cells without the ACE2 receptor. It is thought that this receptor may also be an integrin.[6]

According to World Health Organization (WHO), most of the cases are men. The common age group is between 25 and 64 years, and most of the deaths occur between 65 and 84 years. In the light of the International Severe Acute Respiratory and Emerging Infection Consortium, the female sex is protective, and old age, chronic heart/lung/kidney disease, diabetes, obesity, chronic neurological disorder, malignancy, and moderate-severe liver disease are risk factors for mortality.[7-10] Lymphopenia, leukopenia, and thrombocytopenia are associated with poor prognosis. Neutrophil/lymphocyte and neutrophil/CD8+ T-cell ratio can be used in terms of the severity of the inflammatory response. The depth of lymphopenia correlates with the severity of the disease. Interleukin-6 (IL-6) and D-dimer are used together to predict hospitalization and out-of-hospital mortality (96.4%).[11]

It was shown that neutralizing antibodies against SARS-CoV-2 began to form in the first week and plateaued in the second week in 175 patients with COVID-19 who recovered.[12] In another study, virus-specific immunoglobulin G was found to be low (P = .005) in the acute phase and decreased neutralizing antibody levels in 81.1% of asymptomatic cases compared to 62.2% of symptomatic cases during the recovery phase.[13] Natural infection initiates B- and T-cell immunity; however, the durability of immune protection is uncertain.

In medical wards, patients with an oxygen saturation of equal or lower than 92% are suggested to initiate oxygen treatment via face mask or low-dose oxygen treatment with up to 60% of FiO_2 via venturi mask. Nasal cannula is not recommended. If oxygen saturation is equal or lower than 92% and/or dyspnea persists, intensive care unit (ICU) transfer is required. In a multi-center study from Italy, the results of non-invasive ventilation (NIV) implementation in 679 patients with COVID-19 were presented. Intubation rates in high-flow nasal cannula, continuous positive airway pressure (CPAP), and NIV patients were 29%, 25%, and 28%, and mortality rates were 16%, 30%, and 30%, respectively.[14] In ICU, prone position is suggested if PaO_2/FiO_2 ratio is lower than 150 despite FiO_2 higher than 60%.

Regarding the antiviral treatment, there is not enough evidence of remdesivir to decrease mortality.[15,16] Hydroxychloroquine was shown to prolong hospital stay and to have no effect on 28-day mortality. Moreover, higher invasive mechanic ventilation requirement and death rates were reported in patients treated with hydroxychloroquine.[17] No prognostic advantage was shown with lopinavir–ritonavir treatment compared to standard treatment.[18] The WHO recommended not to use hydroxychloroquine and lopinavir–ritonavir in light of these reports. When it comes to anti-inflammatory drugs, systemic corticosteroids are the only treatment options proven to decrease mortality.[19] Convalescent plasma therapy may be recommended only in critical patients. Anticoagulants are recommended at least in prophylactic dose in all hospitalized patients and in treatment dose in the ICU.[20] There is no evidence of the efficacy of systemic antibiotics in patients with COVID-19.

The effects of COVID-19 on children and adults with chronic respiratory diseases were discussed in the "COVID-19 with Premorbid Respiratory Disease Session." Around 5.5% of the children with cystic fibrosis (CF) required intensive care, and the mortality was 2.1%.[21] Disease effects are similar in children with asthma and adults with asthma who do not require systemic steroids compared to the healthy population of the same age. In chronic obstructive pulmonary disease (COPD) patients with COVID-19, the risk of septic shock, acute respiratory distress syndrome (ARDS), and bacterial co-infection is significantly increased.[22] Interstitial lung diseases (ILDs) increase the

MAIN POINTS

- Novel messages of the European Respiratory Society 2020 are summarized in this article.
- Coronavirus disease 2019 was a major topic of this year's congress.
- Artificial intelligence-based research is progressing in the field of thoracic oncology.
- Interstitial lung diseases and gene-based studies attract attention.

risk due to lung damage, respiratory dysfunction, and immunosuppressive treatments. Coronavirus disease 2019 has a more severe course, especially in lung cancer patients and other cancers that have metastasized to the lung.[23]

The "Post-COVID Session" focused on follow-up and rehabilitation processes after hospitalization, palliative care, and long-term effects of COVID-19. Comorbidities are very common in people with severe COVID-19 infection. These patients should be evaluated for palliative care as long as their symptoms persist. Continuous oxygen therapy is recommended for patients whose oxygen saturation falls below 90%. Opioid therapy is recommended for patients whose dyspnea does not regress despite optimal treatment.[24] New lesions on lung imaging, diffusion disorder, and loss of total lung capacity may develop even 3-4 weeks after the treatment.[25] Hospitalized patients should be comprehensively evaluated after 6-8 weeks and personal pulmonary rehabilitation plans should be structured.[26]

In smokers compared to non-smokers, hospitalization, severe disease course, and mortality rates due to COVID-19 are higher.[27] It is suggested that smoking can increase the cellular uptake mechanisms of SARS-CoV-2 through α7-nAChR signaling. A possible α7-nAChR downstream mechanism could be the induction of phospho-Akt and phospho-p44/42 MAPK. Smoking can affect the pathophysiology and clinical outcome of COVID-19 in various organ systems, including the brain.[28]

PEDIATRIC RESPIRATORY DISEASES

Congenital thoracic malformations can occur by various mechanisms and can affect different tissues in the lung. Patients with congenital thoracic malformation should be followed up for infection, pulmonary hypertension, pulmonary functions, and malignancy (especially congenital pulmonary airway malformation).[29] The frequency of post-infectious bronchiolitis obliterans (PIBO) is gradually increasing. Especially, adenovirus infection and history of previous severe infection are important clues in diagnosis. Although there are different approaches in PIBO treatment, the exact and effective treatment is not known.[30] Low respiratory functions early in life pose a risk for respiratory problems throughout life.[31] Regular follow-up of children with positive airway pressure therapy and sleep-disordered breathing is important for increasing patient compliance, learning device features, and determining the process of leaving the device.[32]

There are different guidelines in asthma management in children. Although Global Initiative for Asthma (GINA) is the most renewed guideline, none of these guides offers the most appropriate approach. Treatment responses may also vary among asthma patients. It is recommended to examine and treat comorbid conditions such as obstructive sleep apnea, gastroesophageal reflux disease, and obesity that may accompany asthma.[33] The primary goal of asthma treatment is to control asthma symptoms and prevent attacks.[34]

Updates on the management of lung infections, pancreatic and liver diseases, new treatments of CF and challenges in treatment adherence, and social and emotional well-being of CF patients are discussed in the session of updates in CF. With current studies, there is a trend toward creating CF transmembrane conductance regulator (CFTR) modulator therapies, while reducing the effects of CFTR protein dysfunction is aimed in traditional treatment of CF. As a result of studies conducted with the use of CFTR modulator, a decrease in hepatobiliary complications, reductions in liver steatosis, decreases in the frequency and severity of acute pancreatitis, and increase in exocrine pancreatic functions is observed.[35-38] Additionally, they have shown that it increases the levels of forced expiratory volume in 1 second (FEV1), decreases the number of attacks, and decreases sweat chlorine levels.[39-43]

RESPIRATORY INFECTIONS

Factors associated with antibiotic resistance and factors related to the use of innate immunity to increase antibiotic efficacy, ways to determine the optimal treatment dose to eliminate infections and prevent the development of antibiotic resistance, and treatment methods of the biofilms were discussed. The highlights are listed subsequently. Having C-reactive protein above 50 mg/dL is significant in deciding to start the antibiotics. Azithromycin reduces the number of bacterial colonies (cfu/min) of infections caused by klebsiella and acinetobacter, which have multiple drug resistance. P2Y12 inhibitor ticagrelor is protective against *Staphylococcus aureus* bacteremia and decreases mortality rates. The use of oseltamivir in methicillin-resistant *S. aureus* bacteremia decreases the mortality. Hyperbaric oxygen therapy allows bacterial proliferation which can increase the sensitivity to the antibiotics.[44-47] In patients with CF, inflammation develops early before infections. The early onset of mucoobstructive inflammation in CF patients is closely related to lung injury.[48] As the life span increases, the frequency of both the complications related to the disease and the complications expected with aging increases.[49]

The WHO's emergencies on tuberculosis (TB) were also discussed. Considering cases with multi-drug-resistant TB in Europe and human immunodeficiency virus/antiretroviral treatments in sub-Saharan Africa, simplifying TB would be very risky. Today, COVID-19 is the most important health issue threatening the world; however, this pandemic is estimated to make a 5-year regression in trials on TB.

Management, new guideline recommendations, and important developments of community-acquired pneumonia (CAP) were discussed in 1 session. The most important factor in the selection of antibiotics for CAP is local epidemiological data of microorganisms and their resistance profiles.[50] It is necessary to consider the alternative diagnosis in unresolved CAP, and if necessary, bronchoscopy, bronchoalveolar lavage (BAL), and histopathological examinations can be applied. The faster detection of causative pathogens using molecular methods results in appropriate antibiotic selection.[51] An immunosuppressive disease should be considered in patients with a history of hospitalization for CAP 2-3 times a year. Around 20-30% of immunosuppressive patients are hospitalized with the diagnosis of CAP, and most of these patients are followed up in ICUs.[52]

Thoracic Oncology

In the article titled "ESR/ERS Statement paper on lung cancer screening," in which 26 authors from 15 European countries

evaluated the current approach and important points in lung cancer screening, the latest developments were summarized in line with the algorithms.[53] Adequate diagnostic quality, volumetric evaluation of nodules, and computed tomography (CT) protocols with as low radiation dose as possible are recommended.[54] It is possible to evaluate nodules with as little radiation as possible by using Artificial Intelligence (AI) to detect nodules in computer-aided diagnostic evaluation and malignancy identification.[55] While solid nodules can be evaluated well in ultra-low-dose CT imaging, nodules with ground-glass density may not be sufficiently differentiated.

Nodules detected by imaging do not show signs or symptoms; they are detected as solid nodules between 5 mm and 30 mm and 23-36%. Imaging-guided biopsy should be considered in solid nodules larger than 8 mm or semi-solid nodules with a doubling time of less than 600 days and a malignancy risk above 10%.[56] Transbronchial technology has evolved from fluoroscopic bronchoscopy to radial Endobronchial ultrasound, electromagnetic navigation bronchoscopy, three-dimensional (3D) imaging with cone-beam computed tomography, and robotic procedures. Biofluids-based candidate biomarkers are circulating tumor cells, circulating tumor DNA, cell-free DNA, messenger RNA, micro RNA, proteins/peptide fragments, metabolic products, volatile organic compounds. Tumor-educated platelets are one of the new biomarkers in liquid biopsies. Radiomics is a stepwise process depending on AI. They both are highly promising. Artificial intelligence-based applications make a difference in lung cancer screening. Key applications are computer-aided detection, radiomics, and radiogenomics.[57] Computer-aided detection systems can detect lung cancer at an early stage but can be useful as a second reader.

The follow-up and treatment plan of ground-glass opacities that can be viewed as pure ground-glass and semi-solid ground-glass nodules should be made according to the morphology of the nodule. A minimum of 5 years of follow-up should be done at intervals of 6-12 months for pure ground-glass nodules and 3-6 months for semi-solid ground-glass opacities. Biopsy should be considered if there is an increase in size and/or density (solid component) of more than 2 mm.

The relationship between the lung cancer microenvironment and the lung microbiome, the role of immunotherapy in small cell lung cancer, and the management of dyspnea and pain in thoracic malignancies were discussed. The microbiota change (the presence of *Ruminococcaceae*- and *Agathobacter*-enriched flora) before and after immune checkpoint inhibitors in advanced stage Non-small cell lung cancer patients is associated with overall survival.[58] It was mentioned that first-line durvalumab plus etoposide with either cisplatin or carboplatin (platinum-etoposide) showed a significant improvement in overall survival versus platinum-etoposide alone in patients with extensive-stage small cell lung cancer (ES-SCLC) in the Durvalumab ± Tremelimumab in Combination With Platinum Based Chemotherapy in Untreated Extensive-Stage Small Cell Lung Cancer Trial study.[59] Updated results of the same study support the use of durvalumab plus platinum-etoposide as a new standard of care for the first-line treatment of ES-SCLC.[60,61]

Screening lung cancer has been shown to reduce lung cancer-related deaths. However, it is necessary to plan capacity needs for the workforce, technological equipment, and facilities.[62] Surgical treatment is safe after neoadjuvant immunotherapy in oligometastatic non-small cell lung cancer in early or locally advanced stage, with promising results. Combined immuno-chemotherapy studies are ongoing.[63,64] In patients with small cell lung cancer with good performance, an increase in survival has been shown with twice-daily radiotherapy, concurrent chemotherapy, and prophylactic cranial radiotherapy.[65] The successful results of integrating oncology and palliative care have been demonstrated. Not only improved quality of life but also longer survival and less aggressive end-of-life care were seen.[66] Thoracic malignancy patients with COVID-19 have higher mortality compared to the other population. In the COVID-19 in patients with thoracic malignancies Trial study, better survival was demonstrated in patients who received steroids or anticoagulants before diagnosis.[67]

Interstitial Lung Diseases

Severe pulmonary sarcoidosis was discussed in a single session. Pulmonary fibrosis is the most powerful indicator of mortality on sarcoidosis. Pulmonary function tests (PFT) can show the effect of fibrosis by low pulmonary functions. On the other hand, fibrosis may appear instead of normal PFTs. Disease severity not only depends on staging but also involved organ numbers, especially cardiac involvement is important.[57] Black race, Human leukocyte antigen-DR3 negativity, lupus pernio, chronic uveitis, age at onset >40 years, splenomegaly, cystic bone lesions, myocardial involvement, and central nervous system involvement are poor prognostic markers. In a study, risk identification has been made by composite physiological index (CPI) which is a clinicoradiological staging system predicting the strongest mortality. An optimal CPI threshold of 40 units was identified. The CPI40, main pulmonary artery diameter to ascending aorta diameter ratio (MPAD/AAD), and an extent of fibrosis threshold of 20% were combined to form a staging algorithm. If CPI >40 or CPI ≤40 with MPAD/AAD >1 or extent of fibrosis on High-resolution computed tomography >20%, it means high risk or poor prognosis. If CPI ≤40, MPAD/AAD <1, and extent of fibrosis on High-resolution computed tomography <20%, it means low risk or good prognosis.[68] Prognosis may be worse if the patient needs treatment at the time of the diagnosis. Preventing silence myocardial damage, treating myocardial inflammation, and sustaining long-term treatment effect should be targeted.[69]

The effects of genetic disposition, particle size, environmental factors in idiopathic pulmonary fibrosis (IPF) and microbiome effects on immunity were discussed in the "air pollution with ILD: a call to arms" session. Genetic predisposition and environmental pollution increase the risk of developing pulmonary fibrosis.[70] Particles smaller than 2.5 microns in diameter reach the alveoli and cause ILDs. In IPF, alveolar epithelial cell damage, apoptosis, and epithelial–mesenchymal transformation can occur.[71] In IPF, air pollution is directly related to low Forced vital capacity, rapid decrease in Forced vital capacity values, and IPF acute attack.[70] There are many factors such as "air pollution" that affect lung microbiome, and they cause acute and chronic diseases.[72]

"Human ex vivo models of ILD" symposium was discussed to present models of early events of IPF ex vivo and the use of these models in evaluating pathogenesis. Human 3D ex vivo lung tissue cultures (generated from precision-cut lung slices) are exposed to a fibrotic cocktail of growth factors and cytokines to replicate IPF. The model represents a valuable tool to assess anti-fibrotic mechanisms of potential drugs for the treatment of IPF patients.[73] Induced pluripotent stem cell models have heterogeneity. To counteract this, the group has used a computation-based approach to single-cell RNA sequencing and Wnt modulation. This emerging technology allows for indefinite expansion of induced type II alveolar epithelial cells (ATII) in culture and provides a guide for improving directed differentiation to ATII which can be used to model ILD and other lung diseases and screen for novel drug therapies.[74] Immortal cell lines answer to generic biological questions such as how the expression of a mutant surfactant protein C results in mistrafficking and causes ATII dysfunction. Lung-on-chip models are a promising tool that may provide insights into new therapeutic targets and enable animal-free preclinical drug testing.[75]

There are some commonalities in the genetics of ILDs. Genetic mutations, telomere shortness, and surfactant protein mutations provide information in the investigation of lung transplantation and mortality.[76,77] In terms of MUC5B, chronic hypersensitivity pneumonia profile is very similar to IPF. When the honeycomb appearance was examined, it was observed that hypersensitivity pneumonitis (HP) results had the same poor outcome as those of IPF patients.[78] When integrative diagnosis of ILDs with clinical and radiological data is insufficient, lung biopsy methods remain an important diagnostic step.[79,80]

Pulmonary Vascular Diseases

Pulmonary hypertension in early life was discussed in 1 session. Female sex is the strongest risk factor for pulmonary arterial hypertension (PAH).[81,82] However, the prognosis in men is worse than in women.[83,84] There are differences in gender-related response to PAH treatment.[85] Loss of signaling in the BMP9/BMPR2/ALK1 pathway plays a central role in the pathobiology of PAH.[86] Patients with idiopathic, sporadic, or hereditary PAH are likely to carry genetic mutations in BMPR (29%) and/or similar genes.[87] The incidence of developing PAH in BMPR2 gene mutation carriers is 2.25% (3.4% in women and 1% in men).[88] Bronchopulmonary dysplasia (BPD) is also a risk factor for PAH and infants with moderate-severe BPD should be screened for PAH because of the unfavorable effects on prognosis.[89,90]

Airway Diseases

There are many causes and diseases that cause or may be associated with chronic cough (CC). In the presence of unexplained or refractory CC, the diagnosis of "cough reflex hypersensitivity syndrome" should be kept in mind. Traditional treatments such as morphine, gabapentin, and pregabalin can be hardly tolerated due to their side effects. With gefapixant, a P2X3 blocker, positive results are obtained especially in the treatment of idiopathic CC. It has been shown to be effective in low doses, and its side effect of taste disturbance is more tolerable.[91] Speech and language therapies are also beneficial in patients with speech impairment due to cough.[92]

Mild and severe asthma treatment and neutrophilic asthma phenotype were discussed in a symposium. Short-acting beta-2 agonist (SABA) should not be given alone to asthmatic patients over the age of 12 years; inhaled corticosteroids (ICS) treatment should be given regularly or in the presence of symptoms.[93] Severe asthma could be divided into 2 phenotypes as T-helper 2 (Th2) and non-Th2 asthma.[94] Biological therapies primarily target Th2 asthma and are indicated in patients with exacerbations or regular Oral corticosteroids use. Today, anti-IgE (omalizumab), anti-IL-5 (mepolizumab, reslizumab), anti-IL5 R (benralizumab) Ant, and IL4/13 (dupilumab) are used in the treatment of severe Th2 asthma. Their predictors have been defined and should be included in pretreatment evaluation.[95]

Use of low-dose ICS has been reported to reduce mortality in asthma.[96] High short-actingSABA use is an important risk factor in asthma exacerbation. In the study called An Overview of Short-Acting β2-Agonist Use in Asthma in European Countries, it has been shown that increased use of SABA is associated with death and exacerbations in asthma.[97] Repeated oral corticosteroid use in uncontrolled severe asthma causes comorbidities such as obesity, diabetes mellitus, obstructive sleep apnea syndrome (OSA), and hypertension. Instead of using chronic oral corticosteroids in patients with severe asthma, treatments such as mepolizumab, benralizumab, and dupilumab should be kept in mind according to the phenotypic evaluation recommended in the last step in the GINA guideline.[98] Long-term use of treatment options, including ICS, increases the risk of pneumonia. According to the Single Inhaler Triple Therapy vs dual therapies Trial study, a higher incidence of pneumonia is seen in treatment groups containing ICS than in the long-acting muscarinic antagonist /long-acting beta-2 agonist group.[99] If the eosinophil count in the blood is >300 in patients with COPD, it is stated as a strong recommendation to continue using ICS. Conditional discontinuation of ICS is recommended in patients with eosinophil count <300 in the blood and less than 2 exacerbations per year. There was limited evidence if the patient had a blood eosinophil count of <300 and more than 2 episodes per year or had 1 hospitalization. In this case, the individual patient's risks and benefits should be discussed and decided.[100]

The future of bronchiectasis management was discussed too. Considering new meta-analysis proving benefit in terms of exacerbation and time to first exacerbation, long-term macrolide antibiotics for the treatment of bronchiectasis in adults is recommended even in patients with colonization of *Pseudomonas aeruginosa*.[101] Inhaled antibiotics are also recommended in adult brochiectasis patients in order to control frequency of exacerbations, especially with high bacterial load and frequent exacerbations.[102] Mucus concentration is shown to be associated with bronchiectasis extend, bacterial load, and inflammation, while MUC5AC/MUC5B ratio is associated with disease severity in bronchiectasis patients.[103] Classification of bronchiectasis patients according to endotype and inflammatory patterns are important due to different potential treatment modalities. Neutrophil elastase

airway test is a newly defined test to assess severity and exacerbation risk in bronchiectasis patients.[104]

Respiratory Critical Care

Diagnosis and treatment strategies and algorithms for ILD in the intensive care were discussed in the "ILD Patients in the ICU Session." Extracorporeal membrane oxygenation is a life-saving option for patients with ILD and acute respiratory failure (ARF), provided they are candidates for lung transplantation.[105] Computed tomography signs of fibrosis predict poor survival in all patterns of ILD-ARF.[106] Bronchoalveolar lavage in the clinical assessment of ARF-ILD is often performed with only a 13% yield.[107] Open lung biopsy in ARDS provided a specific diagnosis in 84% of patients and altered management in 73%.[108] The evaluation of likely reversibility is the cornerstone in the management of ILD patients in ICU.

As the pandemic progressed, intensive care mortality rates have decreased and several risk factors for mortality were identified.[109] Contrary to popular belief, non-invasive mechanical ventilation and high-flow nasal oxygen systems were shown to be safe in terms of viral transmission.[14] In resource-limited settings, even basic supportive treatment options like oxygen therapy were problematic.[110]

Diagnostic strategies in the ICU were discussed in the "Respiratory Critical Care Session.'' Currently, imaging methods, bronchoscopy, and microbiological culture are used for diagnostic purposes. New diagnostic tests that have been developed to be available in the near future are divided into 2 methods, namely imaging methods and biological technology. Imaging methods are quantitative/dynamic ultrasound and confocal lung endoscopy. Biological methods are breath analysis and omic technology in BAL. Confocal lung endoscopy provides information about in vivo pathology. Breath air analysis is quick and reproducible. It has been shown that metabolites in exhaled air can be used in the diagnosis of ARDS.[111] Comprehensive omic analysis is more diagnostic, providing insight into the snapshot of the disease.[112] Although it is not known whether the lung microbiome is a new therapeutic target for the prevention and treatment of ARF, it is one of the important topics that need to be investigated.

Sleep and Breathing Disorders

Obstructive sleep apnea syndrome is a common, multifactorial disease with significant mortality and morbidity but is still underdiagnosed and under-treated. With personalized treatment in OSA, causal treatments for pathophysiology, symptomatic treatment for symptoms such as excessive daytime sleepiness, insomnia, and result-oriented treatments for comorbidities can be planned. In personalized treatment, the patient's upper airway morphology, arousal threshold, loop gain, and muscle response are important.[113] Intermittent hypoxia triggers hypertension, inflammation, endothelial dysfunction, hyper-coagulation, and atherosclerosis.[114] It has been reported that CPAP therapy can significantly reduce the risk of adverse cardiovascular events and stroke among patients using CPAP for more than 4 h/night.[115] If drivers with a diagnosis of OSA have regular use of CPAP for ≥4 h/night and 70% of all nights and there is no excessive sleepiness during the day, it is appropriate to issue or renew their driving license.[116,117]

Sleep and exercise have a bidirectional interaction with each other with a variety of consequences through complicated inflammatory, endocrinological, and neurological mechanisms in acute and chronic stages. Sleep loss results in decrease in physical performance and recovery and increase in exercise-induced diseases. Meanwhile, moderate-intensity aerobic physical activity increases sleep time and slow-wave sleep.[118] The decreased VO_2 max and the impaired heart rate response point an impairment in cardiopulmonary exercise test capacity, which is an important indicator of cardiopulmonary functional capacity and mortality.[119] Comorbid factors such as obesity and cardiac diseases also have potential influences on these associations.[120] In patients with OSA, abnormal blood pressure response is reported and is influenced by obesity.[121] Physical activity has an important role in preventing both OSA and hypertension but requires objective measurement. Aerobic exercise combined with non-invasive mechanical ventilation treatment in OSA patients improves daytime blood pressure.[122] Since physical activity prevents cardiovascular and metabolic diseases in OSA patients, it should be regarded as a part of multicomponent individualized treatment in patients with sleep disorders.[123]

Lung Health

As people age, a decrease in lung capacity, antioxidant activity, anti-aging molecules, and the innate immune system is observed. On the other hand, an increase in autoantibodies, neutrophil and macrophage activities, and inflammatory mediators are observed. Lung capacity increases every year until the age of 25 and reaches maximum capacity at the age of 25, and after that, lung capacity is lost every year. Oxidative stress and smoking increase the rate of lung capacity loss.[124] Lung diseases arise as a result of genome instability, cellular aging, and mitochondrial dysfunction due to telomere wear.[125] Cellular aging contributes to the deterioration of progenitor cell function. Fibrotic mediators affect cellular aging. It is necessary to define specific senotherapeutics and aging biomarkers for chronic lung diseases.

Occupational burden of nonmalignant respiratory diseases was discussed in light of the recent American Thoracic Society/ERS statement.[126] Respiratory conditions of concern were COPD, chronic bronchitis, asthma, IPF, pulmonary alveolar proteinosis, TB, CAP, and granulomatous lung diseases, including sarcoidosis and HP. Weighted summary estimates were calculated from population attributable fraction (PAF) and occupationally attributable burden values and were presented with their 95% CI. The results demonstrated the substantial role of workplace environment in the burden of several lung diseases and were as follows: asthma (PAF, 16%); COPD (PAF, 14%); chronic bronchitis (PAF, 13%); IPF (PAF, 26%); HP (occupational burden, 19%); other granulomatous diseases, including sarcoidosis (occupational burden, 30%); pulmonary alveolar proteinosis (occupational burden, 29%); TB (occupational burden, 2.3% in silica-exposed workers and 1% in healthcare workers); and CAP in working-age adults (PAF, 10%). Among occupational exposures organic (i.e., cotton, grain) and inorganic dust (i.e., coal, silica), cadmium and ambient air pollutants (i.e., Vapors, Gases, Dusts, or Fumes [VGDF]) were the most established causes of COPD. Avoidance from exposure is essential in the management of

patients with work-related conditions. The physician should also consider the socioeconomic aspects.

Normal lung development is necessary to achieve maximum lung health in adulthood.[127] Prenatal factors, genetic factors, and factors in early childhood affect lung development.[128] Maternal asthma, paternal asthma, childhood asthma, maternal smoking, and childhood respiratory infections were significantly associated with lower FEV1 and defined as "childhood disadvantage factors."[129] People who are disadvantaged at an early age have permanently lower lung function. The impact of childhood disadvantage is as great as the impact of heavy smoking.[129] Decreased respiratory function expiratory flow is expected when parents smoke in infancy.[130,131] Like any other organ, the lungs also age.[132] Physiological lung aging is associated with anatomic and functional changes that result in a progressive decrease in expiratory flow rates with age in otherwise healthy people.[132] The incidence of COPD and IPF (2 common chronic respiratory diseases) increases with advanced age. It is plausible, therefore, that abnormal regulation of the mechanisms of normal aging may contribute to the pathobiology of both COPD and IPF.[132]

Managing frailty in patients with acute or chronic lung disorders is mentioned. Frailty can be defined as a highly heterogeneous medical syndrome that defines a state of reduced endurance characterized by decreased physiological functions, which increases the risk of physical dependence and/or death of an individual for various reasons.[133] Components of frailty defined by Fried et al[134] include unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity. Frailty is common in patients with COPD (10.2 %).[135] Muscle satellite cell function is lower in COPD patients compared with age-matched controls, type 1 and type 2 muscle fiber capillarization is decreased, and the distance between the muscle satellite cell and the closest capillaries is increased.[136,137] Frailty can be prevented or reversed through rehabilitation.[138]

The symposium titled "successful stories on improving the delivery of tobacco-use treatment" was chaired by Jorden Vestbo and Sofia Bela Ravara. One of the highlights of the session was Ottawa Model for Smoking Cessation (OMSC) in primary setting.[139] The model aims to give smoking cessation interventions to hospitalized patients in primary settings. The followed methods of the project includes: (1) identification of all smoker patients at hospitalization, (2) documentation of their smoking status, (3) initiation of smoking cessation pharmacotherapy for bedside within hours of application, and the ideal was stated to be starting immediately, and (4) performing face-to-face follow-ups during hospitalization and after discharge by phone for 2-6 months. The studies have shown the effectiveness of the model and that the model is currently being followed by most of the hospitals in Canada.[140] In conclusion, considering the disrupted smoking cessation delivery to outpatient clinics in our country due to the pandemic, the successful example of OMSC looks clinically relevant and applicable.

CONCLUSIONS

This article was created by the detailed analysis of the ERS International Congress sessions and the compilation of their key points. Scientific meetings for 2020 were disrupted due to the pandemic. It was important that pioneering congresses were held virtually. Therefore, updated information on respiratory developments as well as on COVID-19 has been collectively presented in this study. It is important to provide up-to-date information collectively in today's world of rapid scientific developments. The studies in this direction will increase even more in the future.

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Review

ERS International Virtual Congress 2021: Highlights from the Turkish Thoracic Society Early Career Members

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Abstract

This review aimed to highlight some important points derived from the presentations of the European Respiratory Society 2021 Virtual International Congress by a committee formed by the Early Career Task Group of the Turkish Thoracic Society. We summarized a wide range of topics including current developments of respiratory diseases and provided an overview of important and striking topics of the congress. Our primary motivation was to give some up-to-date information and new developments discussed during congress especially for the pulmonologists who did not have a chance to follow the congress. This review also committed an opportunity to get an overview of the newest data in the diverse fields of respiratory medicine such as post-coronavirus disease 2019, some new interventional and technologic developments related to respiratory health, and new treatment strategies.

KEYWORDS: European respiratory society, congress, respiratory diseases, highlights
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INTRODUCTION

The committee formed by the Early Career Task Group of the Turkish Thoracic Society closely followed the European Respiratory Society (ERS) congresses and summarized the prominent issues from the perspective of young academics since 2020. European Respiratory Society Congress 2021 was held virtually because of the coronavirus disease 2019 (COVID-19) pandemic. The ERS congresses have always been a good opportunity to follow advances and new research areas in the pulmonology area. Virtual congresses have some advantages such as easier participation, higher number of physicians capable of following the sessions even after live sessions with recordings. But also, face-to-face interactions are always our first choice. Especially, young pulmonologists at the beginning of their careers may have a chance to meet the leading names, network with peers, as well as participate in their sessions through the congress.

This article reviewed carefully selected sessions to touch main topics including respiratory critical care, airway diseases, post-COVID lung diseases, pulmonary rehabilitation, interventional pulmonology, thoracic oncology, pulmonary vascular diseases, sleep disorders, interstitial lung diseases (ILDs), infectious diseases of the lung, and pediatric respiratory diseases at the ERS Congress 2021. The Early Career Task Group Members of the Turkish Thoracic Society (ECM-Early Career Members) closely followed the congress and summarized the selected sessions. We aimed to identify key points of the congress from the eyes of early career members. So, we thought that some pulmonologists who had no chance to participate in the congress could reach the highlights and updates altogether.

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Respiratory Critical Care

A wide variety of sessions about respiratory critical care were presented at the ERS Congress 2021. The first session was a guideline session that started with the presentation about the physiologic rationale for the use of a high-flow nasal cannula (HFNC) in acute respiratory failure and clinical pitfalls. High-flow nasal cannula is a ventilatory support device that consists of a flow meter giving current up to 60 L/min, an air-oxygen mixer, and an active humidifier. It improves gas exchange, decreases work of breathing and respiratory effort, and provides comfort with a nasal interface. It improves oxygenation and ventilation through 3 important mechanisms:[1-3] (1) by reducing respiratory effort with the flow, (2) by facilitating recruitment with the positive end-expiratory pressure effect provided by the high flow and improve oxygenation, and (3) by reducing the dead space by providing effective clearance of the tracer gas in the upper airways. Although the improvement of oxygenation, reduction of respiratory rate, and respiratory effort with helmet-noninvasive ventilation (NIV) in hypoxemic patients are better, delirium, accumulation of secretion, patient–ventilator asynchrony, patient self-inflicted lung injury (P-SILI) are some problems that arise due to the use of NIV.[4,5] The risk of P-SILI seems to be lower with HFNC.[4] During the pandemic, HFNC has been widely used to prevent pressure-related complications such as pneumothorax and pneumomediastinum in progressive disease in patients. Besides these positive effects, failure of HFNC might cause delayed intubation and worse clinical outcomes.[6]

The second session was a symposium about acute respiratory distress syndrome (ARDS). Acute respiratory distress syndrome is a very heterogeneous picture that develops due to many reasons. It is stated that categorization of the disease into subtypes may be useful in a systemic way. They determined 3 groups according to cytokine clusters, SOFA (Sequential Organ Failure Assessment) score, and gene expressions: (1) adaptive type is due to lymphocyte activation, (2) endothelial leak type is due to isolated respiratory deterioration and related with low serum albumin level, and (3) neutrophil-induced type is leading to multi-organ failure. Mechanically, there are different types of ARDS, their clinical course is different, and treatment must be individualized.

MAIN POINTS

- This study gives an overview of the newest data in the diverse fields of respiratory medicine.
- Post-coronavirus disease 2019 was attractive, and the management was discussed extensively.
- New technologies including algorithmic decision systems-based managements, electronic monitoring devices, health applications, machine learning algorithms, and artificial intelligence algorithms ultimately targeting the benefit of the patient were discussed accordingly in the new era.
- Personalized medicine and management of the diseases were offered.
- Respiratory medicine is one of the most related fields with environmental changes that were pointed out during congress.

A high PaO_2/FiO_2 ratio indicates an improvement in ARDS prognosis. Factors that increase mortality in ARDS and COVID-19 are low PaO_2/FiO_2, high peak pressure, low pH, low platelet count, low bicarbonate, and high ventilation rate.[7] Different treatment modalities are being developed for different patients with multimodal phenotypes.

The third session was a skills lab session about continuous positive airway pressure (CPAP), non-invasive ventilation, and mechanical ventilation. In the evaluation of a confirmed COVID-19 pneumonia patient, due to the poor prognosis in the clinical course, first CPAP with a helmet mask, then invasive mechanical ventilation, extracorporeal membrane oxygenation, and tracheostomy were performed to follow-up patient. With the prone position application, ventilation/perfusion compliance, reduction of transpulmonary pressure, improvement of right ventricular function, and removal of weight pressure from the lung are provided.[8] It is recommended to avoid Non-invasive mechanical ventilation (NIMV) in de novo respiratory failure and viral conditions. In addition, correct positioning of tracheostomy ensures less granulation tissue. Before the tracheostomy is opened, it should be checked that there is no obstruction in the upper airways by imaging. Tracheostomy should be performed after good ventilation settings and effective tracheal suction. In the next process, the time without mask should be increased gradually. Cough should be increased with high-frequency chest wall oscillation and intrapulmonary percussive ventilation. In the rehabilitation and physiotherapy approach after acute respiratory failure, there is an algorithm in which all patients are mobilized.[9] It is aimed to perform physiotherapy in order to ensure that patients wean from ventilation, with at least 50% maximal inspiratory pressure of respiratory muscle strength.

Airway Diseases

Recent clinical advances in airway diseases were also presented, and new treatment strategies were discussed during the congress. For the patients with asthma who are not controlled by high-dose inhaled corticosteroids (ICS), adding tiotropium reduces exacerbations and improves lung function.[12] Airflow obstruction was significantly reduced with the addition of tiotropium, as compared with the addition of placebo as a result of the study. At 24 weeks, the mean difference between the tiotropium group and the placebo group in the change in the adjusted peak forced expiratory volume in 1 second (FEV_1) from baseline in the first 3 hours after the administration of tiotropium was 86-154 mL higher significantly. As per Global Initiative for Asthma (GINA), in track 1 in step 4 high-dose ICS is not recommended. Adding long-acting muscarinic antagonists (LAMA) is recommended for this group. In track 2, there is an option for step 4, which is high-dose ICS. For step 5, add-on LAMA is recommended to medium or high-dose ICS-LABA. There is a question about the efficacy of triple therapy in one single inhaler. New GINA, in track 1, offers low-dose ICS-formoterol at every step as-needed reliever therapy. Also in track 2, step 1 recommends ICS whenever short-acting beta-agonists (SABA) are taken. Budesonide-formoterol is more effective than salbutamol both in terms of exacerbation preventation and asthma control even in mild intermittent asthma.[13]

Over the last 60 years, the inhaler technique of patients has not improved.[14] Suboptimal use of inhalers affects clinical efficacy. True inhalation technique increases lung deposition. ACT on Inhalers (Access, Choose, and Train) is an algorithm for tailoring the right inhalation device. It is based on asking the patient if he/she takes a slow and steady breath or a quick and deep breath. If the patient can perform slow and steady, we should consider a metered-dose inhaler, soft mist inhaler, or breath-actuated inhaler; if the patient can perform quick and deep breath, we should consider a dry powder inhaler. After choosing the device, we should teach the inhaler technique to the patients.[15]

Some updates about inhalers in the COVID-19 pandemic were also presented. Cleaning the inhaler mouthpiece, spacers, or peak flow and not sharing the inhalers with anyone has been suggested. We should prefer pMDI+spacers for SABA instead of aerosol-generating procedures like nebulizers.[16] There are smart inhalers, also referred to as e-inhalers, which have sensors, Bluetooth connection linked to an app. They may be the way forward. Most e-inhalers monitor dose usage and inhalation profile hence providing real-life feedback on inhalation technique.[17] These connected inhalers may help to solve inhaler technique problems, improve adherence, and provide early detection of exacerbations by monitoring inhalation volumes.

New treatments for chronic cough were also discussed. After excluding and treating obvious causes, refractory unexplained idiopathic chronic cough existed. There are studies about standard care for refractory chronic cough with low-dose morphine and gabapentin with substantial side effects and risk of abuse and addiction. New therapies are focusing on P2X3 receptors and pathways and block these receptors at the larynx and airways. P2X3 antagonism with Gefapixant provides a 75% reduction in cough; however, all the patients complained of taste disturbance.[18] Second-generation P2X3 pathway antagonists including sivopixant and eliapixant are more effective in trying to avoid taste adverse effects. Other mechanisms that may be effective in chronic cough are voltage-gated sodium (Na V) channel blockers and airway sensory nerve blockers. Nebulised lidocaine that blocks Na V channels is also effective.

Lung Health

Environmental changes have some causal relationships between adverse environmental exposures and respiratory outcomes. Strategies to decrease the burden of resulting respiratory diseases have been discussed during the congress. The interactions of poverty and environmental exposures as an additional "new" risk for respiratory health, new World Health Organization (WHO) Air Quality Guidelines (AQG), which are based on the expert evaluation of the latest scientific evidence on the health effects of air pollution, what potential implications the new WHO AQG will have on the air quality legislation in European Union, which is in the heart of European Green Deal, and how respiratory clinicians can use the new guideline in their clinical work were some important points of the presentation.

Sex and hormonal influence on respiratory diseases and if we need a gender-specific approach for health interventions were other questions discussed during the congress. Some hot points are as follows: females have smaller lungs and airways compared to males of the same height in adulthood, stronger immune response, and a higher incidence of autoimmune diseases.[19] Asthma is more prevalent in young boys, but after puberty, more severe and prevalent in women.[20] Estrogen seems to induce airway inflammation while androgens may reduce. Women have a greater susceptibility to chronic obstructive pulmonary diseases, more severe disease with earlier onset, a higher risk of hospitalization and death from respiratory failure and comorbidities, and a faster annual decline in FEV_1 even when they smoke fewer cigarettes.[21]

Societies identify certain roles, behaviors, activities, attributes, and opportunities for women, men, boys, girls, and people with non-binary identities.[22] Gender is a social determinant of inequality as well as being effective on its own. Gender norms and expectations influence exposure to unhealthy products, care-seeking, health protection patterns, and whether people smoke. Gender inequalities worsened during the COVID-19 pandemic. Globally, tobacco use is associated with gender, and exposure to passive smoking is more pronounced in females.[23]

Adolescents are experimenting with various types of nicotine-containing products. In the United States, 35% of high school students use ≥2 nicotine products at the same time. The most frequent ones are electronic cigarettes (EC) and small cigars.[24] Among 14-17 years olds, EC use ranges between 5% and 39%.[25] Nicotine and cannabis use can induce significant long-term deficits in the developing brain by interfering with the cholinergic regulatory processes.[26] Cannabis is a risk factor for bronchial asthma or the use of asthma medication even when known risk factors are taken into consideration.[27] It can also cause serious lung diseases with increasing years of use. There are behavioral interventions for smoking cessation in young people. Studies applying a single intervention can be grouped by theoretical basis: stage of change models, motivational interviewing, and social cognitive theory.[28] The most important strategy for countries is to protect children from starting smoking and/or vaping. Pricing and smoke-free policies combined with regulations that restrict youth access to nicotine products are the major strategies proven to prevent and reduce tobacco use for young people.[29-31]

New technologies in respiratory health are in the upcoming rising situation that is pointed out during the congress, and ethics, risks, and patients' perspectives were discussed. Algorithmic decision systems-based management has some risks such as digital divide differences, sample bias, systemic bias, automation bias (from the doctor), decrease in trust, pressure to meet objectives, continuous competition with others, threat to internal motivation, threat to autonomy, loss of accuracy over time, and threat to the environment. Electronic monitoring devices are considered the current gold standard, facilitate patient self-management, and provide intervention for compliance. The COVID-19 pandemic has led to a rapid increase in the use of home monitoring in patients with a variety of chronic respiratory conditions.[32] Real-time monitoring of heart rate, oxygen saturation, and respiratory rate is possible with wearable technologies. Sensors can detect

cough and other respiratory sounds.[33] Health applications can be used interactively for monitoring treatment use, symptom tracking, providing environmental data to help prevent triggers, and asthma education.[34] Recent technological advances offer an opportunity to improve the care of children with respiratory diseases.

Machine learning algorithms can process and assimilate data from large numbers of patients, far greater than the ones a single physician can manage and comprehend in an entire career.[35] Machine learning approaches are used for predicting asthma and chronic obstructive pulmonary disease (COPD) exacerbations.[36] The COVID-19 pandemic has brought about the widespread use of digital tools in all aspects of our lives. It should be strongly highlighted that the final decision and responsibility for all medical decisions remain in the hands of the treating physicians, supported by the computing power of the artificial intelligence algorithm, ultimately targeting the benefit of the patient.

Pulmonary Vascular Diseases

Optimal outpatient in acute pulmonary embolism (PE), treatment and prophylaxis applications in cancer-related venous thromboembolism (VTE), comparison between interventional treatments in PE and systemic treatments, imaging methods in pulmonary arterial hypertension risk classification, and some special situations were discussed during the congress. Cancer is a risk factor for VTE, but cancer screening is not routinely recommended after acute PE; screening is recommended in patients who cannot find a provoking cause for PE.[37] It has been shown that there can be an increased risk of VTE in patients who has anaplastic lymphoma kinase mutations in lung cancer (LC). It may be important for personalized risk assessment.[38] Real-life studies suggest that individualized therapy may have potential advantages.

The risk of recurrent embolism and bleeding in cancer-associated thrombosis (CAT) is higher than in non-cancer-related VTE.[39] Low-molecular-weight heparin comes to the fore in CAT treatment and prophylaxis, as it has a lower risk of a recurrent embolism when compared to vitamin K antagonist and the risk of bleeding may be higher with direct oral anticoagulants.[40] Thrombolysis increases the risk of major bleeding and stroke although it may prevent hemodynamic decompensation and reduce mortality in patients with medium-high risk PE.[41,42] Although half-dose thrombolytic treatment is effective and causes less bleeding complications, additional treatment and higher costs can be required.[43] Ultrasound-assisted thrombolysis (USAT) and ultrasound at the catheter tip can separate fibrin threads and allow better penetration of tissue plasminogen activator. But there was no difference in terms of results while comparing between USAT and catheter-directed thrombolysis, and USAT was more costly.[44] Catheter-directed thrombolysis can provide effective treatment with less bleeding risk in medium-high risk PE, and the superiority of USAT is still controversial.

There are 3 steps in the treatment of recurrent VTE: to confirm the diagnosis of recurrent VTE, to determine the cause, and to change/escalate therapy. The residual disease is frequent. Over 50% of patients have residual deep vein thrombosis (DVT) or PE imaging abnormalities >6 months after treatment.[45-47] This leads to many false-positive results. We must compare current imaging to past imaging if we suspected acute recurrent VTE. Risk assessment for pulmonary arterial hypertension is also important in the follow-up of PE. Risk assessment can be performed without invasive methods and may facilitate routine follow-up.[48] Risk assessment based on cardiac magnetic resonance imaging was found to be equivalent to right heart catheterization in the 1-year follow-up.[49]

Pediatric Respiratory Diseases

Bronchiectasis, a chronic lung disorder, is an umbrella term used for a clinical syndrome of recurrent or persistent wet cough, airway infection/inflammation, and abnormal bronchial dilatation on chest computed tomography (CT) scan. Bronchiectasis may be reversible over time with effective treatment, therefore, early recognition is important.[50,51] Bronchiectasis is not considered rare but is an overlooked lung pathology with high economic cost and poor quality-of-life (QoL) in children/adolescents and their parents.[52] However, all likely etiologies involve airway infection causing inflammation, impaired mucociliary clearance, and airway destruction.[53] High-resolution multidetector chest CT with high-resolution CT (HRCT) is used instead of conventional HRCT to diagnose bronchiectasis in children/adolescents.[54] Respiratory exacerbation is defined when a child/adolescent has increased respiratory symptoms (predominantly increased cough ± increased sputum quantity and/or purulence) for longer than 3 days. When dyspnea and/or hypoxia is accompanied, it should be considered a severe exacerbation. Regular airway clearance techniques are recommended; however, recombinant-human DNAse, bromhexine, inhaled mannitol, and hypertonic saline are not recommended for routine usage.[50,55] Anti-asthma agents should not be used routinely. During an acute respiratory exacerbation, a systemic course of an appropriate antibiotic is used for 14 days. For patients who have recurrent exacerbations, treatment with long-term macrolide antibiotics has been shown to reduce exacerbations.[56,57] Surgery should be performed rarely and only in the specialized center in patients with no recurrent localized disease.[58] Parents of children/adolescents with bronchiectasis must be informed about the disorder and get an active role in the disease management.

Asthma is the most common chronic respiratory disorder that affects approximately 9.4% of children in the European Union.[59] International asthma guidelines and individual country guidelines are inconsistent, which results in confusion in the diagnosis of asthma. There is no single gold standard test to confirm the diagnosis. The Task Force (TF) of the ERS guidelines for diagnosing asthma in children aged 5-16 years is not recommended as it is diagnosing asthma based on symptoms alone. The TF recommended measuring fractional exhaled nitric oxide (FeNO), performing spirometry, using bronchodilator reversibility test in children with abnormal spirometry, and doing a direct bronchial challenge test as a part of the diagnostic work-up of children aged 5-16 years with suspected asthma; however, it is not recommended to use skin prick test, serum total and specific IgE tests, peak expiratory flow rate variability testing as a primary objective.[60,61]

Severe asthma remains uncontrolled despite high-dose ICS-LABA treatment of contributory factors or needs high-dose

ICS-LABA to prevent becoming uncontrolled. T2-high inflammation of the airway means high production of IL4, IL13, and IL5. Current biologics for severe T2-high asthma: Anti-IgE: Omalizumab, it is available for > 6 years; anti-IL5/anti-IL5R: mepolizumab, age > 6 years; benralizumab, age > 12 years; reslizumab, age > 18 years; anti-IL4R α blocking IL4+IL13 receptor: dupilumab, age ≥ 12 years. Omalizumab has additional effects on viral asthma exacerbation.[62] Treatment evaluation is recommended after 4-6 months. All biologics reduced exacerbation nearly to 50%. In the future, new biologics are expected to be developed with alarmins. Alarmins are proteins coming from epithelial cell layers with different triggers like pollution and smoking. Auto-alarmins are IL-33 and IL-25, which have broad effects. Before starting biological treatment be convinced that patients had severe asthma and T2-high inflammation has been demonstrated by high eosinophils, FeNO, or IgE. The transition of care from childhood to adulthood is important. New non-invasive biomarkers are needed.

Treating asthma by endotypes may be more successful. Prednisolone is very useful in the treatment of chronic asthma, provided the sputum contains a large number of eosinophils, and in the absence of eosinophilic sputum, it is not effective enough.[63] In preschool wheeze, ERS TF defines 2 patterns: episodic (viral) wheeze (EVW) and multiple-trigger wheeze (MTW). These 2 are in 2 different mechanisms. Montelukast can be started when symptoms of viral cold develop for EVW, and maintenance treatment with ICS should be started for MTW as trial therapy and should be stopped when there are no benefits.[64] However, phenotypes can switch over time.[65] Four pathophysiological clusters (endotypes) were identified in recurrent severe preschool wheeze; atopic, non-atopic with non-infection rate and high ICS use, non-atopic with high infection rates, non-atopic with low infection rate, and no ICS.[66] In young children with asthma, biomarkers may be useful for guiding treatment selection. Sensitized patients and patients with eosinophilia (≥300 cells/μL) have good responses to ICS.[67]

Stridor is a symptom of airway narrowing, whether it is purely inspiratory or purely expiratory (wheezing) or a group "in-between" characterized with different breathing sounds and complex airway anomalies. Physicians usually evaluate upper airways to assess the nasal cavity for congestion, atresia, adenoids, tonsils, pharyngeal collapse, vocal cord movement, obstruction, reflux disease, laryngomalacia, fistula, and cleft with the airway endoscopy. Severe laryngomalacia and laryngeal cleft are often accompanied by swallowing issues and airway breathing problems and may need swallowing therapy or surgery. Laryngotracheal stenosis is related to multiple comorbidities and a high degree of pulmonary disease. For complex airway cases, upper airway and pulmonology follow-up program is suggested, and after the surgery, pulmonary function tests should be performed for follow-up.

Lung involvement in sickle cell disease (SCD) includes acute chest syndrome, asthma, recurrent wheezing, pulmonary fibrosis and restrictive lung disease, hypoxemia, sickle chronic lung disease, sleep-disordered breathing, and pulmonary hypertension. Pulmonary complications are the major cause of morbidity and premature death. Recurrent acute chest syndrome episodes may lead to sickle cell chronic lung disease, and lung function deteriorates with the increasing age. Acute chest syndrome which starts with the vaso-occlusive crisis has a high mortality rate if there is a delay in diagnosis, and treatment is divided into supportive care (oxygenation, prevention of atelectasis, intravenous fluids, analgesia) and modifiable factors (bronchodilators, transfusion, respiratory infection). Airway obstruction and bronchial hyperreactivity are more prevalent in patients with SCD and may be independent of asthma. Obstructive lung function abnormalities also reflect pulmonary vascular abnormalities. Hypoxemia should also be promptly treated as it triggers red cell sickling and acute or chronic complications. Hydroxyurea treatment and long-term home oxygen therapy are recommended in these cases. Hematopoietic stem cell transplantation and gene therapy are curative in SCD.[68,69]

Interventional Pulmonology

Interventional pulmonology session described new diagnostic and therapeutic techniques and procedural aspects with detailed videos. Robotic bronchoscopy combined with needle-based confocal laser endomicroscopy for peripheral LC enables real-time microscopic imaging of cells and is a helpful tool for the diagnosis of LC in the absence of endobronchial abnormalities. External sheet enables the fiberoptic bronchoscope to move safely to peripheral lesions, and endomicroscopy enables visualizing malignant cells. The accuracy of this technique is between 89% and 95%.[70]

Endobronchial valves for lung emphysema help reduce hyperinflation in COPD patients resulting in better FEV1 % predicted, 6-minute walking test, and quality of life. Placing endobronchial valves is a relatively safe procedure, and reported complications are as follows: pneumothorax 10-33%, expectoration of valves 5%, and granulation tissue formation 10%.[71]

Target lung denervation for COPD targets parasympathetic nerves and aims to reduce airway hyper-responsiveness, mucus secretion, and inflammation. With this technique, the epithelium of the bronchus is protected, and controlled radiofrequency energy is delivered. Results from AIRFLOW 1 and 2 indicate that moderate or severe exacerbation rates are reduced in treated patients.[72,73]

Cryobiopsy in ILDs has a similar diagnostic yield with surgical sampling in ILDs but has advantages on length of stay in hospital and complications.[74-76] Sampling should be done from 2 separate sites and patients with increased pneumothorax risk should be monitored carefully. New innovative guidance systems like radial ultrasound, CT-fluoroscopy, and navigation systems are described within this session.

First-line treatment for localized LC is surgery, but medical comorbidities prevent surgery in 10-25% of the patients. Percutaneous radiofrequency ablation of LC was described in 2004 and was recommended in ACCP/STS (American College of Chest Chest Physicians/Society of Thoracic Surgeons) consensus 2012. However, bronchoscopic radiofrequency ablation is relatively very new. It was shown that it is a safe and feasible option, appears to achieve well-targeted and complete ablation zones.[77] The efficacy of this procedure is still being investigated.

Rheoplasty in chronic bronchitis aims to control symptoms in chronic bronchitis by reducing goblet cells and goblet cell hyperplasia.[78] Recent studies performed to the fifth- to seventh-generation of airways to carina showed improvement in CAT and St. George's Respiratory Questionnaire (SGRQ) scores.

The first use of shape-sensing robotic bronchoscopy system for solitary pulmonary nodules smaller than 2 cm in 2019 showed safety with 96.6% target nodule reach and sampling.[79] Another study presented in congress showed biopsy completion in 98% of cases.

Endobronchial ultrasound combined with endoscopic ultrasound through esophagus for a complete endoscopic staging of LC increases diagnostic yield and is currently considered as an optimal non-surgical mediastinal staging tool for LC.[80,81]

Interstitial Lung Diseases

According to the official ATS/ERS/JRS/ALAT Guideline about idiopathic pulmonary fibrosis,[82] there are 4 terms: usual interstitial pneumonia (UIP), probable UIP, indeterminate for UIP, and alternative diagnosis. Radiologically, subpleural (anterior in upper lobes and posterior in lower lobes) and basal dominant honeycombing demonstrates UIP. If other features are similar, but there is no honeycombing, the term probable UIP is eligible. It has been emphasized that findings can be asymmetric in these 2 patterns. Indeterminate for UIP category includes patients with subpleural and basal predominant subtle reticulation and features and/or distribution of lung fibrosis that do not suggest any specific etiology. In addition, it has been mentioned that the positive predictive value of HRCT diagnosis of UIP pattern for pathological UIP pattern is 90-100%. However, diagnosis of UIP patterns is not easy and needs a multidisciplinary evaluation.

It was shown that there are persistent functional alterations and persistent HRCT opacities even 12 months after severe COVID-19 pneumonia.[83] Risk factors for this severe persistent condition are male, older age, increased body mass index, the severity of the initial injury, traction bronchiectasis at discharge, and some blood markers. KL-6, leucocyte telomere length, cytokine cocktail, 50-gene signature, fibrocyte ratio at the time of diagnosis, and 9 weeks evaluation of MMP7, HGF, LCN2 are determined risky blood markers.[83-86] LCN-2 is associated with epithelial injury, MMP-7 is related to epithelial injury and fibrosis, HGF is a marker of epithelial repair.[87] It has been shown that nintedanib does not affect survival but provides shorter ventilation duration and increases ventilator-free days.[88]

During the session, early post-COVID ILD was discussed, and the features of the early auto-inflammatory phenotype were mentioned. Histopathologic findings are consistent with lymphoid inflammation and organizing pneumonia in most cases, and patients are responsive to corticosteroid treatment.[89,90] The mechanism of this period is related to the immuno-inflammatory cascade, invasion of the epithelial and endothelial components. Hence, immunomodulation and anti-thromboembolism prophylaxis has been offered during the presentation.[91] There are two-hit hypotheses, genetic predisposition or pre-existing ILD and pro-fibrotic cascade. There is an indication to treat with anti-fibrotic drugs only in cases of disease progression despite immunomodulation, and cases are clinically reclassified as IPF (idiopathic pulmonary fibrosis) or progressive fibrotic ILDs.[82,92,93] Take-home messages of this presentation were about the percentages of post-COVID ILD, unknown clinical significance, different phenotypes, possible underlying auto-inflammatory background, and importance of immunomodulatory therapies.

Another session was about LC associated with fibrotic ILD (fILD). Interstitial lung diseases are a variety of parenchymal lung diseases that have various origins and causes, related either to inflammation or to fibrosis. Associated comorbidities highly influence morbidity and mortality, and one of them is LC. When the IPF group and non-IPF ILD group were compared, the incidence of LC was found higher in the IPF group, all suggesting that fILD has increased risk for LC development.[94] Risk factors for cancer in fILD have been identified in different studies as older age at diagnosis, smoking, emphysema, male gender, and rapid annual decline in forced vital capacity. So, it is suggested that there might be a connection between the fibrotic process and carcinogenesis. Squamous cell carcinoma is the most frequently encountered cancer in fILDs, whereas it is adenocarcinoma in the general population. Cancer survival is worse in patients with fILD. Cancer stage, treatment options like surgery, chemotherapy, and radiotherapy cause IPF exacerbations thus increasing disease severity and mortality.[94]

Some molecular biology markers indicating dysplasia in IPF are also observed in lung carcinomas and invasive tumors of other parts of the body, such as the BRAF (B-Raf proto-oncogene) pathway.[95] With these findings, IPF could be considered not mainly a fibrotic disease but also a bronchiolar epithelial proliferation that the lung parenchyma is rebuilt by basal bronchiolar cells. The honeycombing change may be considered a pre-neoplastic lesion.

All treatment options for LC have a major risk of triggering acute IPF exacerbations. But with a major anti-fibrotic protective effect, more effective cancer therapy in LC-fILD can be achieved, and this strategy could improve survival in LC-fILD cases. There is no human data on anti-fibrotic therapy reducing the risk of radiation pneumonitis, and there is uncertainty on chemotherapy for lung cancer in IPF because of the pulmonary toxicity.

Sleep Disorders

It is not an appropriate approach to evaluate obstructive sleep apnea (OSA) cases with different phenotypes with the same diagnostic technique and to evaluate them with the same treatment method.[96] The clustering approach is important for the treatment of homogeneous groups defined for personalized medicine. Obstructive sleep apnea cases are clustered according to their characteristics such as age, degree of obesity, the severity of sleep apnea, sleepiness, smoking habit, and the burden of comorbidities is evaluated. Phenotypes are associated with cardiometabolic risk and treatment response. Apnea–hypopnea index (AHI) was defined at thresholds to classify the disease severity of OSA,[97] and AHI has no correlation with Patient and Parent Epworth Sleepiness Score,[98] health-related QoL, and also objective sleepiness on Multiple Sleep Latency Test (MSLT).[99]

Mild OSA is highly prevalent with 25% of the general population having AHI 5-15.[100] Symptom profile especially sleepiness has no association with sleep disorder breathing severity measured by AHI.[101] Continuous positive airway pressure benefits sleepiness and QoL but there is no convincing evidence that active therapy of mild OSA affects comorbidities.[102] Pathophysiology of cardiometabolic complications of OSA is still incompletely understood, and intermittent hypoxia is likely the key factor. It has a unique pattern rather than other chronic lung and cardiac diseases and activates proinflammatory pathways.[103-105] Basal, minimal SpO_2, and percentage of sleep under SpO_2 < 90% Total Sleep Time (TST), and oxygen desaturation index (ODI) are used for predicting intermittent hypoxia. The hypoxic burden is a new marker for intermittent hypoxia calculated by the total area under the respiratory curve for individual apnea and hypopnea and divided into total sleep time.[106] Hypoxic burden predicts cardiovascular mortality better than AHI and ODI.[107]

Physiological sleepiness is defined by a biological drive to sleep which can be measured by MSLT, pupillography, and electroencephalography. Manifest sleepiness that involves behavioral signs of sleepiness, performance deficit on psychomotor or cognitive tasks can be measured by maintenance of wakefulness test, vigilance, and performance test. Introspective sleepiness which is how the individual self-assesses sleepiness can be measured by sleepiness scoring systems.[108] Excessive sleepiness at the time of OSA diagnosis may not resolve after CPAP treatment. Residual sleepiness in sleep apnea patients treated with CPAP therapy was more prevalent in patients with moderate OSA than in patients with severe OSA and was not associated with diabetes or cardiovascular disease. Residual sleepiness was more prevalent in low compliance groups. Patients with residual sleepiness should be evaluated with other possible causes of excessive daytime sleepiness (EDS) (obesity, diabetes, mood disorders, drug/alcohol use, anemia, hypothyroidism, neurologic disorders). Residual EDS should be assessed at least after 3 months of CPAP treatment, and other causes of EDS excluded, before starting drug therapy.

The P4 medicine (prediction, prevention, personalization, and participation) is an evolving approach to personalized medicine for OSA. Prediction determines whether patients with OSA will benefit from treatment and respond to therapy. Prevention is divided into primary, secondary, and tertiary. Personalization includes diagnosis and management of OSA. Participation contains patient-centered outcomes. To approach OSA with an integrative approach, subgroups should be well defined.[109] The clinical clusters were provided an opportunity for a more personalized approach to the management of OSA.[110]

Telemedicine can be used in diagnosis, consultation phases and CPAP education, titration, and follow-up period for patients with sleep breathing disorders (SBD).[111] Despite potential clinical interest, literature remains scarce because of the complexity of the procedure. In the upcoming years, new measurement indexes other than the AHI will be important, and miniaturized and wearable devices will become part of the SBD diagnosis.[112,113] In a global view of integrating management for CPAP patients, telemonitoring by PAP devices and smartphone applications for coaching education and engagement are going to take an important place in improving not only adherence but also the quality of care.[114]

Thoracic Oncology

Repair and regeneration in chronic lung disease and lung cancer sessions were presented, and it has been mentioned that lung cancer is a syndrome, not a disease. Various mutations are seen in lung cancer subtypes, most commonly in adenocarcinoma. Environmental, hereditary, and replicative factors are effective in mutations.[115] KRAS, TP53, and some mutation signatures are more common in smokers with lung adenocarcinoma (LA).[116] In mouse models of LA developed by tobacco and chemical exposure, it has been shown that club cells in the airway are also involved in the tumor, in addition to alveolar cells. Again, KRAS mutations were observed in club cells in mice, and it was observed that these cells were the origin of lung cancer with tobacco exposure.[117] While club cells, bronchoalveolar stem cells, and alveolar type 2 cells are involved in transgenetic LA models, club cells are primarily involved in those originating from tobacco exposure. Affected by environmental exposure and genetic mutations, these cells can also be targeted therapeutically.

The extracellular matrix (ECM) consists of various connective tissue elements, mainly collagen, elastin, and fibronectin. Lung fibrosis is characterized by increased deposition in the ECM and changes in cell remodeling and attachment. Proteins associated with ECM-derived pathological gene expressions were more produced in fibroblasts in IPF.[118] Extracellular matrix content also varies in asthmatic patients. It has been shown that fibulin-1 expression is increased in these patients and is associated with exaggerated proliferation.[119] Fibulin-1 regulates TGF-ß activity by binding to LTBP-1. Especially the absence of fibulin-1C is protective against chronic asthma and pulmonary fibrosis.[120]

Currently, 4000 lung transplantations are performed each year. However, due to the difficulties in finding donors, there is a need to explore different options. Human tissues can be produced with the 3D bioprinting method; however, there is a need for the development of bioinks for more advanced and complex structures. Reinforced with ECM derived from decellularized tissue is a bioink developed for the production of small airways. It promotes cell differentiation and minimizes tissue rejection. Studies have shown that it is biocompatible in T-cell-immunodeficient and -immunocompetent mice. It also supports vascularization in the full graft.[121] It is promising for the future of lung transplantation.

Repair damage is one of the important factors in the development of COPD. Regenerative approaches play an important role in the course of diseases. Mesenchymal stem/stromal cells regulate properties such as immunomodulation, tissue repair, and antimicrobial activity in lung tissue with the factors they secrete, and it has been reported that they may be useful in the treatment of emphysema.[122] Stimulating lung progenitor cells supports alveolar differentiation and provides tissue repair.[123]

Respiratory Infections

Community-acquired pneumonia (CAP) in the post-COVID era and updates on pneumonia including critical analysis

of the new guidelines and new diagnostic and therapeutic options in light of recent experience with COVID-19 pneumonia were discussed in the session. The microbiologic etiology of CAP in the adult population in the United States and Europe remains undetected in nearly 2/3 of patients. *Streptococcus pneumoniae* constitutes the majority of detectable pathogens. Difficulties in obtaining samples from the lower respiratory tract, the effect of antibiotic use before sample collection, and low sensitivity of some diagnostic tests are some possible reasons that might explain the difficulties in identifying the etiology of pneumonia.[124]

Prevalence of multidrug-resistant (MDR) organisms in CAP diversifies by region and by pathogens, 3% MRSA-CAP,[125] 1% MDR *Pseudomonas aureginosa* CAP.[126] Inappropriate use of antibiotic therapy contributes to the development of drug resistance, excessive costs, and increased mortality.

The antibacterial pipeline is dominated by derivatives of established classes and most of the display-limited innovation. Nonetheless, new antibiotics including ceftaroline and ceftobiprole, which are from the cephalosporin group; solithromycin from the macrolide group; nemonaxacin and delafloxacin from quinolone group, lastly omedacycline and lefamulinare are currently under development to treat CAP.[127]

The mortality rate due to CAP is highly significant. Depending on the patients who are in septic shock or need IMV, mortality is highest up to 40%.[128] There are several scoring systems that assess the severity of pneumonia-diagnosed patients. According to the study of Fan,[129] comparing the scoring systems like A-DROP, CURB-65, PSI, SMART-CAP, NEWS2 CRB-65, and Q-SOFA in COVID-19 patients, it is found that A-DROP, developed by the Japanese Society of Pneumology, has the best performance.

Bacterial coinfection is less common in COVID-19 when compared with influenza (33%).[130] Along with COVID-19, increased use of HFNO (High-flow nasal oxygen) due to having more ventilator-free days and a decrease in length of stay in ICU was observed.[131] In a study comparing NIMV and HFNO, it was shown that the intubation and mortality rates were lower in the HFNO subgroup.[132] Moreover, intubations rates are reduced with the help of awake prone positioning.

Along with the H1N1 pandemic, real-time diagnosis has also revealed the presence of viral pathogens. The treatment of viral infections varies and depends on the causative agents. Specific diagnostic tools are required to commence the optimal treatment for patients. With the COVID-19 pandemic, specific analytic patterns including inflammation, superinfection, and thrombosis are detected, which lead to a more personalized treatment strategy.[133]

CONCLUSION

Early Career Members of the Turkish Thoracic Society have closely followed the congress and prepared messages that collectively constituted this paper. One of the rising points during the congress is the importance of personalized therapy which is important to manage diseases. Another point is that, after the COVID-19 pandemic, the application of telemedicine increases in both clinical practice and research providing an opportunity to improve responses to medications, individualize treatment and monitoring, and lower costs. Also, with this paper prepared by the early career members, notes provide up-to-date information and may lead to new scientific research or developments.

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Case Report

COVID-19 Pneumonia After SARS-CoV-2 Vaccination with CoronaVac: A Case Series from Turkey

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Abstract

Coronavirus disease 2019 is a novel viral infection that has caused a pandemic globally. Many kinds of vaccine development studies were conducted to prevent the spread and deaths. The CoronaVac is the most commonly used vaccine in Turkey. Phase 3 trials from various countries revealed that CoronaVac efficacy ranged from 50.7% to 91.25% but increased in moderate or severe cases to 100%. Additionally, it was remarkable owing to high seroconversion rates achieving up to 100%. After the vaccine campaign began in Turkey, critically ill patients continued to admit to our center's intensive care unit though they had been vaccinated with 2 doses of CoronaVac. The clinical course of these patients revealed that they are still at high risk of severe disease and death. Therefore, we aimed to share these patients' clinical characteristics and disease course, laboratory, and radiologic data.

KEYWORDS: COVID-19, CoronaVac, pneumonia, SARS-CoV-2, vaccination
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INTRODUCTION

On December 8, 2019, the researchers defined the first coronavirus disease 2019 (COVID-19) case as unexplained pneumonia in China.[1] Afterward, the disease has spread rapidly, and the World Health Organization (WHO) declared the outbreak as a pandemic.[2] To date, COVID-19 caused more than 4.2 million deaths and almost 200 million confirmed cases worldwide.[3]

The researchers conducted many kinds of vaccine development studies designed in different methods. To date, WHO approved the emergency use authorization for Pfizer/BioNTech, AstraZeneca-SK Bio, Covishield, Janssen, Moderna, Sinopharm, and CoronaVac.[4,5] In Turkey, CoronaVac, Pfizer/BioNTech, and Sputnik V were approved by the Ministry of Health for emergency use.[6-8] CoronaVac is the most commonly used vaccine in Turkey. Studies from different countries determined the efficacy and seroconversion of the CoronaVac in various doses. In phase 1 or 2 trials, the seroconversion rate changed between 92.4% and 100% after 2 doses.[9-12] Additionally, phase 3 trials revealed that CoronaVac efficacy ranged from 50.7% to 91.25%,[13-15] but it increased in moderate or severe cases to 100%.[15]

CoronaVac was initially administered in 2 doses 4 weeks apart to risky groups and individuals over 65 years old in Turkey. Despite the high prevention rates, especially for severe disease, we realized that critically ill COVID-19 patients over 65 years old were still admitted to our center's intensive care unit (ICU) though they had been vaccinated with 2 doses. In this paper, we aimed to assess critically ill COVID-19 cases admitted to ICU after the second CoronaVac dose.

In this case series, we assessed the patients admitted to ICU in a tertiary hospital between March and May 2021 due to COVID-19 after the second CoronaVac dose. Before ICU admission, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acid tests were performed on nasopharyngeal swabs using the reverse transcriptase-polymerase chain reaction (RT-PCR) test for all patients according to the local guidelines.[16] The date of the first RT-PCR test positivity was recorded on ICU admission. All data were collected prospectively. Patient characteristics, laboratory, and radiologic data, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and Charlson Comorbidity Index (CCI) were recorded. Written informed consent was obtained for each case.

The Statistical Package for the Social Sciences Statistics software (SPSS Version 24.0; IBM Corporation, Armonk, NY, USA) was used to perform statistical analysis. The data were expressed as the median and interquartile range for continuous variables and counts and percentages for categorical variables. We did not need any uni- or multivariate analysis.

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Table 1. Baseline Characteristics of the Patients

		Patients								
Patient Characteristics	**All Cases (n = 12)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Age, years	77.0 (71.0-78.5)	76	77	75	78	79	66	84	77	67
Gender	Male, 5 (55.6)	Male	Male	Male	Female	Female	Female	Male	Female	Male
BMI, kg/m^2	28.0 (26.7-32.2)	27.6	41.5	27.3	33.2	31.2	31.1	28.0	26.1	25.6
APACHE II score	16 (12-26)	12	15	19	16	18	11	33	33	10
CCI	5 (4-6)	4	6	4	5	5	4	6	8	2
Smoking history	2 (22.2)	–	N/A	+	+	–	N/A	–	–	–
Comorbidities										
Hypertension	6 (66.7)	+	+	+	+				+	+
Immunosuppression	0 (0.0)									
Diabetes mellitus	4 (44.4)	+	+				+		+	
Coronary artery disease	2 (22.2)				+			+		
Congestive heart failure	3 (33.3)		+		+				+	
Chronic kidney disease	4 (44.4)		+		+	+			+	
COPD	2 (22.2)		+	+						
Malignancy*	1 (11.1)					+				
Cerebrovascular diseases	1 (11.1)						+			
Duration after second vaccine dose, days	29 (17-57)	17	22	17	29	54	7±	60	42	59
Mortality	6 (66.7)	+	+	+	–	+	–	+	+	–

All values are expressed as numbers (percentages) or median (interquartile range).
BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; CCI, Charlson Comorbidity Index; N/A, not applicable; COPD, chronic obstructive pulmonary disease.
*Solid-organ malignancies.
±The patient had a contact history with a person diagnosed with COVID-19 2 days after vaccination.

CASE PRESENTATIONS

We identified 9 cases with COVID-19 diagnosis confirmed by the RT-PCR test. We described their clinical characteristics, disease course (Table 1), laboratory data, and radiologic findings (Table 2).

Patient 1

A 76-year-old male with hypertension (HT), type II diabetes mellitus (DM), hypothyroidism, and retinitis pigmentosa was admitted to the hospital due to falling down at home 17 days after the second CoronaVac dose. The computed tomography (CT) excluded pathologies related to trauma but revealed multilobar involvement in both lungs with multiple subpleural consolidations and ground-glass opacities suspicious for COVID-19 (Figure 1A). The RT-PCR test confirmed the diagnosis. Favipiravir therapy was started. Methylprednisolone was given with a dose of 1 mg/kg/day and discontinued by gradually reducing in 10 days. The patient was transferred to the ICU due to severe hypoxemia 3 days after admission. High flow nasal oxygen (HFNO) and non-invasive mechanical ventilation (NIMV) therapies were applied alternately, but he was intubated on the 10th day. The patient underwent cardiopulmonary resuscitation for 3 minutes after intubation. Seven days after intubation, the patient was diagnosed with ventilator-associated pneumonia (VAP) caused by *Acinetobacter baumannii*. On the 23rd day of ICU admission, the patient died due to septic shock.

MAIN POINTS

- CoronaVac has been approved by many countries and World Health Organization for emergency use to prevent coronavirus disease 2019 (COVID-19), and it is the most commonly used vaccine in Turkey.
- Phase 3 trials revealed that the efficacy of the CoronaVac vaccine ranged from 50.7% to 91.25% but increased to 100% in moderate or severe cases.
- Despite the high prevention rates achieving 100%, especially in moderate and severe cases, critically ill COVID-19 patients vaccinated with 2 doses of CoronaVac are still admitted to the intensive care unit in our center.
- The present data point that patients vaccinated with 2 doses of the CoronaVac are still at high risk and precautions for disease transmission are still essential for these patients.

Patient 2

A 77-year-old male with HT, DM, congestive heart failure (CHF), chronic kidney disease (CKD), and chronic obstructive pulmonary disease (COPD) was admitted to the hospital with complaints of dry cough 22 days after the second CoronaVac dose. Reverse transcriptase-polymerase chain reaction test confirmed the COVID-19 diagnosis. The patient

Table 2. Laboratory and Radiologic Data of the Patients

		Patients								
	All Cases (n = 12)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
RT-PCR positivity	9 (100.0)	+	+	+	+	+	+	+	+	+
Laboratory data*										
WBC, $\times10^3$/μL	14.9 (10.4-19.5)	9.3	14.9	8.2	11.4	13.5	16.9	16.2	31.2	22.1
Neutrophil, $\times10^3$/μL	13.5 (9.8-17.0)	8.9	13.5	7.7	10.7	12.8	15.0	14.4	30.1	19.0
Hemoglobin, g/dL	11.0 (8.9-11.9)	11.8	12.0	11.2	8.1	9.6	14.7	8.7	9.0	11.0
Lymphocyte, $\times10^3$/μL	0.5 (0.3-0.8)	0.2	0.5	0.2	0.4	0.4	0.9	0.7	0.7	1.6
Lymphocyte, %	3.4 (2.3-4.9)	2.3	3.4	2.3	3.8	2.9	5.5	4.2	2.2	7.4
Platelet, $\times10^3$/μL	305 (207-368)	294	330	171	242	305	353	128	383	516
BUN, mg/dL	32.6 (25.5-52.5)	25.0	30.4	39.4	55.0	50.0	26.0	32.6	111.5	22.6
Creatinine, mg/dL	1.42 (0.84-2.43)	1.16	1.42	0.86	2.55	1.68	0.81	2.3	3.03	0.72
Total bilirubin, mg/dL	0.81 (0.67-1.29)	2.04	0.81	1.41	0.61	0.69	0.69	0.65	0.81	1.17
CRP, mg/L	163 (61-310)	323	297	69	352	102	16	163	238	52
AST, U/L	44 (31-75)	49	44	113	17	42	26	35	101	44
ALT, U/L	34 (23-54)	25	34	83	14	28	38	21	46	61
LDH, U/L	453 (348-590)	399	619	560	229	453	480	297	895	431
Ferritin, ng/mL	283 (124-2500)	246	1145	136	112	3854	283	106	9878	418
HS troponin I, ng/L	29 (13-73)	12.0	29.0	29.0	84.0	14.0	6.0	30.5	61.4	145.0
D-Dimer, μg/mL	1.24 (0.67-2.72)	2.17	0.52	0.55	13.02	0.93	1.24	2.68	0.79	2.75
Procalcitonin, ng/mL	0.23 (0.08-1.87)	2.73	0.23	0.09	26.91	0.09	0.06	0.79	1.01	0.07
BNP (plasma), pg/mL	290 (84-854)	290	233	84	854	N/A	N/A	729	3098	73
Arterial blood gas analysis*										
pH	7.43 (7.33-7.51)	7.53	7.43	7.51	7.32	7.43	7.42	7.33	7.23	7.51
$PaCO_2$, mmHg	31 (30-37)	27	32	31	31	29	41	51	30	32
PaO_2, mmHg	52 (47-57)	52	49	56	70	49	57	46	36	57
HCO_3, mmol/L	24.6 (19.0-25.7)	24.6	22.5	26.4	17.0	21.0	25.0	24.9	13.3	26.8
Lactate, mmol/L	2.4 (1.5-2.8)	2.4	2.6	1.6	1.3	1.8	3.0	0.6	4.4	2.6
SO_2, %	88 (85-91)	93	86	89	92	84	88	86	50	89
PaO_2/FiO_2	81 (67-94)	73	82	93	159	75	81	60	60	95
Chest CT compatibility±										
Typical	6 (66.7)	+	+				+	+	+	+
Indeterminate appearance	2 (22.2)			+		+				
Not applicable	1 (11.1)				+					
Chest CT severity										
Mild	0 (0.0)									
Moderate	3 (33.3)	+						+		+
Severe	3 (33.3)		+	N/A	N/A	N/A	+		+	

All values are expressed as median (interquartile range).
RT-PCR, real time-polymerase chain reaction; WBC, white blood cell; BUN, blood urea nitrogen; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; HS troponin I, high-sensitive troponin I; BNP, brain natriuretic peptide; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; SO_2, arterial oxygen saturation; FiO_2, fraction of inspired oxygen; CT, computed tomography; N/A, not applicable.
*Tested on the day of ICU admission.
±Performed on hospital admission.

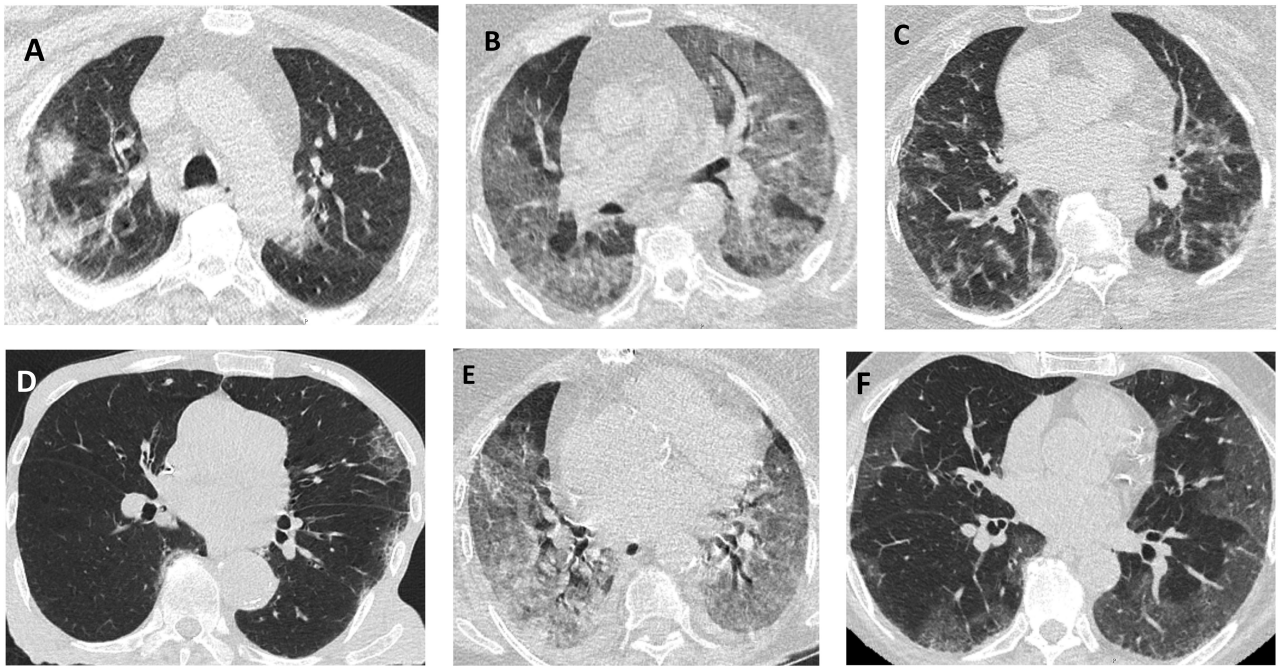


Figure 1. Axial thorax computed tomography findings of the patients are shown in (A-F). (A) Multiple subpleural consolidations and ground-glass opacities, (B) widespread ground-glass opacities and consolidations, (C) ground-glass opacities and reticular densities, (D) subpleural multicentric ground glass opacities prominently in left the lung and diffuse emphysema in both lungs, (E) widespread ground-glass opacities and consolidations in both lungs, and (F) ground-glass opacities and reticular densities prominently in the left lung. CT, computed tomography.

had a mild illness and was discharged home with favipiravir therapy. Two days later, he was readmitted to the hospital with dyspnea, and oxygen saturation (SpO_2) was 85% in room air. Chest CT scan revealed basal-localized bronchocentric nodular consolidations with ground-glass opacities and crazy-paving pattern bilaterally compatible with severe COVID-19 pneumonia (Figure 1B). The patient was transferred to ICU on the day of hospital admission due to respiratory failure. Methylprednisolone was started with a dose of 1 mg/kg/day as an addition to favipiravir. Also, levofloxacin therapy was added empirically. Two days later, the disease progressed, and the methylprednisolone dose was increased by 250 mg/day for 3 days and then decreased to 1 mg/kg/day. On the 14th day, the patient was intubated due to severe hypoxemia. Five days after intubation, he was diagnosed with VAP caused by *Klebsiella pneumoniae*. Additionally, *A. baumannii* was detected in percutaneous blood sample culture. The patient died on the 30th day of the ICU stay due to septic shock.

Patient 3

A 75-year-old male patient with HT and COPD was admitted to the emergency unit with a complaint of dyspnea 17 days after the second CoronaVac dose. On admission, the SpO_2 was 68%. The chest CT scan revealed peripheral ground-glass opacities with the signs of interstitial lung disease and was reported as indeterminate appearance for COVID-19. The reverse transcriptase-polymerase chain reaction test resulted in positive. Then the patient was transferred to the ICU on the day of admission. Favipiravir and levofloxacin were started. Methylprednisolone was initiated with a dose of 250 mg/day for 3 days, then decreased to 1 mg/kg/day, and discontinued by gradually reducing in 10 days. High flow nasal oxygen therapy was started. Despite the HFNO, respiratory failure progressed, and the patient was intubated due to deterioration of mental status. On the 14th day of intubation, the patient underwent bedside percutaneous tracheostomy. The patient died on the 37th day of ICU admission due to septic shock.

Patient 4

A 78-year-old woman with HT, coronary artery disease (CAD), CHF, CKD, and a history of aortic valve replacement was admitted to the emergency unit with a complaint of abdominal pain. Physical examination and laboratory data indicated acute pancreatitis. During the gastroenterology ward stay, the disease became complicated due to acute kidney injury. Before the ICU admission, the RT-PCR test resulted in positive. Although the patient got the second dose of CoronaVac 29 days ago, the RT-PCT test was positive. On the third day of hospital admission, the patient was transferred to the ICU. Favipiravir was initiated for the treatment of COVID-19 and there was no need for methylprednisolone therapy. The patient only needed conventional oxygen therapy during the ICU stay. She was discharged on the sixth day from ICU with no complications.

Patient 5

A 79-year-old woman with CKD was admitted to the emergency unit due to dyspnea. The patient had a history of non-Hodgkin lymphoma diagnosed in 2016, received chemotherapy, and was followed up for 5 years with no recurrence. She also had undergone a mastectomy in 2000 due to breast cancer and used hormone therapy for only 5 years. The chest CT scan indicated consolidations, air bronchograms, ground-glass opacities on the mid-peripheral zones, and bilaterally pleural effusion. It was reported as an indeterminate appearance for the diagnosis of COVID-19 pneumonia. Although the patient was vaccinated almost 2 months ago, the RT-PCR test resulted in positive. Despite routine therapies including favipiravir, methylprednisolone (1 mg/kg/day), anti-biotherapy,

oxygen therapy via non-rebreather reservoir mask, and prone position, the respiratory failure worsened on the seventh day of admission, and the patient was admitted to ICU to provide advanced respiratory therapies. The methylprednisolone therapy was revised with a dose of 250 mg for 3 days and then decreased to 1 mg/kg/day with a discontinuation plan after gradually reducing in 10 days. High-flow nasal oxygen and NIMV therapies were applied alternately. On the seventh day of ICU admission, she was intubated due to refractory hypoxemia. Then, she was diagnosed with acute kidney injury. During the third hemodialysis therapy, she underwent cardiopulmonary resuscitation due to cardiac arrest and did not achieve the return of spontaneous circulation.

Patient 6

A 66-year-old woman with DM and a history of ischemic cerebrovascular event was diagnosed with COVID-19 by RT-PCR test by the filiation team 7 days after the second CoronaVac dose. She had a contact history 2 days after the last vaccine dose with her nephew, who was diagnosed with COVID-19. Favipiravir therapy was started on the day of diagnosis, and 4 days later, the patient was admitted to the emergency department with complaints lasting 2 days of dry cough, back pain, and dyspnea. The chest CT scan revealed a severe involvement with the ground glass opacities and reticular densities in all pulmonary lobes (Figure 1C). Oxygen saturation was 87% in room air. After admission to the pandemic ward, methylprednisolone was started with a dose of 1 mg/kg/day. On the eighth day of the hospital admission, the patient was transferred to the ICU due to severe respiratory failure. Methylprednisolone dose was changed to 250 mg/day for 3 days and then decreased to 1 mg/kg/day with a discontinuation plan in 10 days after gradually reducing. Respiratory support was provided with HFNO and NIMV alternately. On the fifth day of ICU admission, the patient was diagnosed with macrophage activation syndrome, and tocilizumab was administered with a dose of 400 mg once. Gradually, the respiratory support decreased. On the eighth day of ICU admission, respiratory support was converted to conventional oxygen therapy. She was discharged on the 11th day of ICU admission.

Patient 7

An 84-year-old male patient with CAD and dementia who lives at a nursing home was diagnosed with COVID-19 by the filiation team 2 months after the last CoronaVac dose. Favipiravir was prescribed for an ambulatory treatment process. Twenty days later, he was admitted to the emergency unit due to clouding of consciousness and tachypnea. Chest CT scan revealed a moderate pulmonary involvement with diffuse peripheral ground-glass areas more prominent in the left lung and diffuse emphysema in both lungs (Figure 1D). The laboratory tests showed metabolic acidosis with a normal partial oxygen pressure, clearly indicating acute renal failure. The patient needed repeated hemodialysis therapies, and on the fourth day of admission, oxygen therapy was started via a simple oxygen mask due to hypoxemia. On the sixth day of admission, he was transferred to ICU for advanced respiratory support. On the day of ICU admission, methylprednisolone was started with a dose of 1 mg/kg/day, and the patient was intubated due to HFNO failure. On the fifth day of intubation, endotracheal aspirate sample culture indicated VAP diagnosis due to *K. pneumoniae*. Although the administration of appropriate medications according to antimicrobial resistance results, the patient died on the 15th day of ICU admission due to pneumosepsis.

Patient 8

A 77-year-old woman with HT, DM, CHF, CKD, and a history of aortic valve replacement was diagnosed with COVID-19 by the filiation team 42 days after the second CoronaVac dose. She used favipiravir therapy for 5 days, and on the seventh day of diagnosis, she was admitted to the emergency unit due to severe dyspnea. On admission, SpO2 was 78% in room air. There was widespread involvement of bilateral middle and upper lobes in the chest CT scan, including ground-glass opacities and consolidations (Figure 1E). She was transferred to ICU for HFNO therapy on the day of emergency unit admission. Levofloxacin therapy was started. Methylprednisolone was initiated with a dose of 1 mg/kg/day, then increased to 250 mg/day for 2 days, and decreased to 1 mg/kg/day again for 10 days. On the 10th day of ICU admission, the patient was intubated due to altered mental status caused by hypoxemia. The culture of tracheal aspirate samples collected on the day of intubation revealed *A. baumannii* pneumonia, and the patient died on the 13th day of ICU admission due to septic shock.

Patient 9

A 67-year-old man with HT was admitted to the emergency unit due to dry cough and dyspnea 59 days after the second CoronaVac dose. Chest CT scan revealed the ground glass opacity with moderate involvement (Figure 1F), and the RT-PCR test was positive for COVID-19. Favipiravir was started. On the fifth day of admission, methylprednisolone was started with a dose of 1 mg/kg/kg due to increased oxygen requirement. On the eighth day of admission, respiratory failure progressed, and the patient was transferred to ICU. The patient was supported with HFNO, and an awake prone position was provided for at least 12 h/day. Methylprednisolone dose was increased to 250 mg/day for 3 days and then decreased to 1 mg/kg/day. The patient was transferred to the ward without any complication on the seventh day of ICU admission.

DISCUSSION

In the present case series, we assessed 9 critically ill patients with laboratory-confirmed COVID-19 after the second dose of CoronaVac vaccination. The median age of the patients was 77.0 years (71.0-78.5), and most of them were male (55.6%). The median APACHE II score was 16 (12-26). All patients had at least one or more comorbidities, and the median CCI was 5 (4-6). The most common comorbidities were HT (66.7%), DM (44.4%), and CKD (44.4%). None of the patients had immunosuppression. The laboratory data revealed high rates of infectious parameters and decreased global oxygen delivery with a low partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) values. Radiologic findings showed various levels of pulmonary involvement ranging from moderate to severe, but none had a mild involvement. The median duration after the second

dose of vaccination to PCR positivity was 29 days (17-57). Despite the high seroconversion rates up to 100%[9-12] and efficacy rates achieving 100%, especially in moderate or severe cases,[13-15] the mortality was 66.6% in the present data. Additionally, the rate of mortality was relatively similar to a previous study from the same center.[17] The presented data demonstrated that patients vaccinated with 2 doses of the CoronaVac vaccine are still at risk of severe COVID-19, and death and precautions for disease transmission are still essential for these patients.

All patients were vaccinated with 2 doses of CoronaVac. The duration from the second vaccine dose to COVID-19 diagnosis ranged between 7 and 60 days. In phase 1 or 2 trials of CoronaVac vaccine, the seroconversion rates after different follow-up periods such as 14 or 28 days were 97% in healthcare workers,[9] 96.8%-100% in healthy children and adolescents,[10] 92.4%-97.4% in healthy individuals aged between 18 and 59 years,[12] and 95.7%-100% in healthy volunteers aged 60 years or over.[11] None of our cases had a documented seroconversion rate measurement between COVID-19 diagnosis and vaccination. Previous studies determined that the CoronaVac vaccine achieves higher efficacy rates with higher neutralizing antibody levels on the 28th day than on the 14th day after the second dose.[11,12] In this case series, COVID-19 was diagnosed 14 days after the last CoronaVac dose in 8 patients and 28 days after in 5. Additionally, the contact history of the patient 6, 2 days after the last dose of vaccination was notable, although she was diagnosed 7 days after the vaccination with COVID-19.

The phase 3 trials from Brazil, Indonesia, and Turkey showed the CoronaVac efficacy with the rates of 50.7%, 65.3%, and 91.25%, respectively,[13-15] but it increased in cases requiring assistance to 83.7% and in moderate or severe cases to 100%.[15] However, in 8 cases, the disease progressed to severe respiratory failure, and 6 patients died. In the deceased cases, the laboratory and radiologic data revealed severe hypoxemia, decreased global oxygen delivery, a lower PaO_2/FiO_2 ratio than 100 mmHg, and moderate or severe involvement in chest CT images. Additionally, in 2 deceased patients, on ICU admission, a high level of procalcitonin indicating secondary infection was notable.

Recent studies showed that individuals vaccinated with CoronaVac had a reduced neutralizing capacity against the new variants, especially for the B.1.617.2 (Delta) strain.[18,19] However, all patients included in the present case series were diagnosed with COVID-19 between March and May 2021 when B.1.617.2 strain had not been detected in Turkey yet,[20] but the patients in the present case series were not tested to determine any kinds of strain. Thus, any of them might also be an undefined delta variant case from Turkey.

In conclusion, we defined 9 critically ill cases with severe COVID-19, who all were diagnosed after 2 doses of CoronaVac vaccination and presented their clinical characteristics, laboratory, and radiologic data in this paper. Although it is still debating whether CoronaVac is effective against the variants such as B.1.617.2, individuals vaccinated with 2 doses of CoronaVac might also be infected by a non-Delta variant. Also, patients admitted to the hospital due to any reason except COVID-19 may potentially have the risk of asymptomatic COVID-19, though they had been vaccinated with 2 doses of CoronaVac. We hope that the data presented in this paper contribute to improving outcomes of the postvaccination COVID-19 cases. However, it is clear that new randomized, controlled trials are needed on this topic.

Informed Consent: Written informed consent was obtained from the patients or the patients' next of kin who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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Case Report

Xeroderma Pigmentosum-Associated Childhood Interstitial Lung Disease

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Abstract

Chromosomal breakage syndromes are a group of genetic disorders that are ascribable to the autosomal recessive mode of inheritance. Xeroderma pigmentosum is one of the chromosomal breakage syndromes which is due to the involvement of deformity in the deoxyribonucleic acid's nucleotide excision repair. Xeroderma pigmentosum is a genetic disorder, which is autosomal recessive, heterogeneous, and more common in cases of consanguinity, caused by mutations in at least 10 genes and 9 complementation groups. The disorder is very rare. Patients experience photophobia and extreme photosensitivity and have pigmentary changes in ultraviolet light-exposed areas of the body with freckling, premalignant, and malignant skin lesions arising in keratinocytes soon after the fleeting exposure to sunlight. Patients are also oversensitive to environmental mutagens such as cigarette smoke and possibly to the widely used agricultural insecticide, diazinon. Progressive neurological abnormalities along with some rare complications are also noticed among these patients. Symptoms and thoracic high-resolution computed tomography are considered for diagnosis. Only corticosteroids can be given to limit the progression of the disease. Xeroderma pigmentosum-related interstitial lung disease is one of the rarest forms and we thereby report an interesting case.

KEYWORDS: Xeroderma pigmentosum, interstitial lung diseases, corticosteroids
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INTRODUCTION

The interstitial lung disease (ILD) describes a heterogeneous group of chronic disorders comprising of lung parenchyma and alveolar interstitium.[1] Interstitial lung disease in pediatric patients is a varied group of rare respiratory disorders that are usually present in childhood and associated with significant morbidity and mortality. However, the presentation can sometimes be a delayed one and the manifestations may be evident in adolescence or early adulthood. This can be attributed to the slow progression leading to delay in seeking medical care. The pathogenesis of the distinct childhood ILD (ChILD) is complicated and implicates genetic contributors.[2-5] Childhood interstitial lung disease incidence is arduous to assess, probably because the diagnosis remains cryptic in abounding situations without identifiable causes. This is embellished by reviewed prevalence estimates that extend from 0.1 to 16.2 cases per 100 000.[2,4-6] Sometimes the etiology of ILD can be identified to be caused by inorganic and organic exposure, drugs, connective tissue disease, or smoking-related. However, the identification of such a cause is seldom seen in child. The clinical course of the child case is unforeseeable, with a decline in pulmonary functions punctuated by episodes of acute exacerbation.[2,7] Various multisystem genetic disorders may have child as one of their components. Xeroderma pigmentosum (XP) is a rare genetic multisystem disorder affecting skin and lungs and also predisposes the patient to develop distinct malignancies. The elementary pathology in patients with XP is a breakdown of an enzyme involved in nucleotide excision repair (NER). Defective deoxyribonucleic acid (DNA) repair occurs after exposure to ultraviolet light (UV) light, customarily in the range of 290-320 nm or chemical carcinogens. Xeroderma pigmentosum-associated ILD is very rare and can present as microcephaly, cerebellar ataxia, growth retardation, skeletal abnormalities, hypogonadism, pancytopenia, abnormal pigmentation, and immunodeficiency's.[8]

CASE PRESENTATION

A 20-year-old male non-addict, the eighth child of non-consanguineous parents was referred from the medical ward in view of breathlessness to our outpatient department. He had a past history of pulmonary tuberculosis (TB) (presented with hemoptysis) at the age of 4 months old and was managed with anti-tubercular treatment for 1 year. He was symptomatic since childhood with complaints of dry cough, dyspnoea on exertion for 4 months (Modified Medical Research Council-MMRC grade 4), intermittent fever, and history of infective exacerbation 0-1/year, multiple skin pigmentation, and hypersensitivity to sunlight, and thus, he was diagnosed with XP. There was no history of chest pain. He had increased symptoms for 4 months with a complaint of dry cough, increased tremor, history of increased frequency of bowel movements, and intermittent fever. His general examination was within normal limits. Physical examination revealed bilateral crackles, and a 6-minute walk distance could not be performed. On investigation, his hemoglobin level was 13.3 g/dL and his total leucocyte count was 28 000 cells per cubic millimeter of blood, with neutrophils 80% and lymphocytes

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Figure 1. Bilateral reticulonodular opacities.

10%. Other biochemical parameters were within normal limits. Chest radiograph showed bilateral reticulonodular opacities (Figure 1). Serum immunoglobulin-E was 394. Human immunodeficiency virus, hepatitis C virus, hepatitis B virus, and serological tests were non-reactive. High-resolution computed tomography showed intra- and interlobular septal thickening, ill-defined ground glass opacities throughout lung parenchyma, widespread ill-defined centrilobular nodules, and scattered and patchy lobular air trapping (Figure 2). These features were consistent with ILD. As the patient was symptomatic since childhood, relapse TB and lung cancer were excluded as diagnosed clinically and radiologically due to the chronic duration of illness. Two-dimensional echocardiography revealed pulmonary artery systolic pressure of 40 mmHg. Spirometry showed a restrictive pattern with forced vital capacity (FVC) of 9% and Indian predicted (IP) of 10%. The patient was referred for expert neurology opinion to the in-house neuromedicine department, and the likelihood of neurological involvement was excluded by history and clinical examination. Ophthalmology reference was done to rule out squamous cell carcinoma of the eye and he was diagnosed as having early pterygium with prominent blood vessels. We excluded immunodeficiency-related lung infection (Pneumocystis pneumonia (PCP) and many others)

MAIN POINTS

- Xeroderma pigmentosa-related interstitial lung disease (ILD) is one of the rarest forms of ILD.
- The underlying pathogenic mechanism behind this development is based on short telomere abnormality.
- Only corticosteroids can be given to limit the progression of the disease.

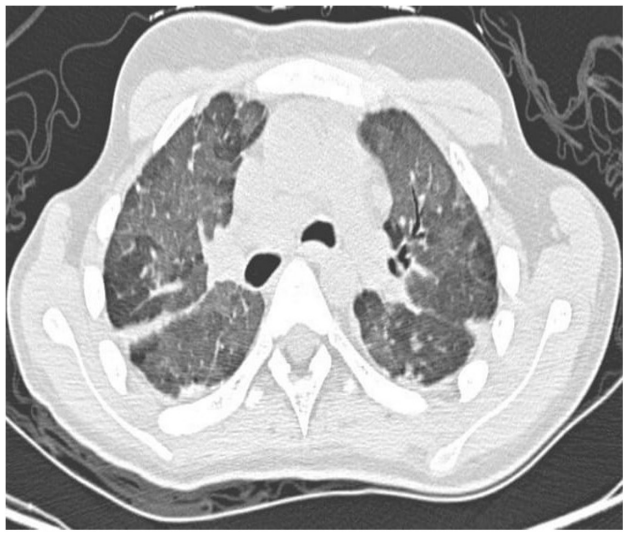


Figure 2. High resolution computed tomography showing honeycombing, septal thickening.

by doing sputum examination for gram smear and culture, fungal smear, and culture and sputum for PCP. Bronchoscopy was planned but was not possible due to the deterioration in the patient's clinical condition. Hematological malignancies were excluded by complete blood count and differential count and by taking expert hematological opinion. However, in view of patient being relatively symptomatic and lung function is very poor, trans-bronchial lung biopsy (TBLB) was not done. The genetic test was not performed due to financial restrictions. The final diagnosis was made as XP-associated ILD which was based on a multidisciplinary approach. Patient was started on tablets prednisolone 30 mg per day for 6 months followed by tapering for total duration of 6 months and fluconazole 200 mg stat followed by 100 mg per day for 10 days in view of XP with oral candidiasis. Patient was a candidate for long-term oxygen therapy and offered the same with other rehabilitation. Within few months after discharge, the patient died shortly at age of 20 years.

DISCUSSION

Xeroderma pigmentosum is an extremely rare autosomal recessive disorder (chromosomal breakage syndrome). It was first described by Moriz Kaposi[2] in 1876. Xeroderma Pigmentosa is divided into eight subtypes with seven caused by a defect in the NER pathway (XPA,XPB,XPC,XPD,XPE,XPF,XPG) while the eighth (XPV) caused by a defect in DNA polymerase.[9] It starts in early childhood and severe changes occur as pigmentary changes in UV-exposed areas of the body and cutaneous photosensitivity. Incessant exposure may result in skin cancer development.[9,10] The skin ages prematurely frequently over sun-exposed area, look dry, and contain both hypo and hyperpigmented regions.[9-11] Our patient was also having multiple skin pigmentation and hypersensitivity to sunlight since childhood. There is a defect in the DNA repair mechanism. In children younger than 3 years, severe changes appear and become progressively more severe. Patients experience photophobia and extreme photosensitivity and have pigmentary changes in UV-exposed areas of the body with freckling, premalignant, and malignant skin lesions. Patients are also hypersensitive to environmental mutagens such as cigarette

smoke and possibly to the widely used agricultural insecticide, diazinon.[8] Patients due to UV radiation exposure are prone to develop central nervous system (CNS) tumors, which manifest as a neurodegenerative process, and other tumors as well. Ultimately landing to have a short life span.[12] Our patient did not have any CNS abnormalities. Further neurodegenerative problems that arise include impaired cognitive ability, ineptitude to walk, hearing loss, delayed sexual development, abnormal speech, and inability to swallow leading to the requirement of a feeding gastrostomy.[9,13] Our patient did not have any impaired cognitive abnormalities; however, he had difficulty walking. Studies also propose that below 20 years, XP patients have an increased risk for brain cancers and those at other CNS locations[14-16] The Peculiarity of XP is related to young-onset and lesion which commence around 2-8 years.[13,14,17] To diagnose XP, DNA analysis is often used helping to differentiate XP from autosomal dominant diseases that could be mistaken for XP including Peutz–Jeghers syndrome, Cockayne syndrome, Leopard syndrome, and Carney complex.[9,11,13] In our patient, we could not do genetic analysis due to financial restrictions. The most common fate for individuals with XP is death from skin cancer, most frequently due to metastatic melanoma or invasive squamous cell carcinoma.[13,14] Patients with XP are 1000 times more prone to skin cancers caused by UV irradiation.[9,18]

Xeroderma pigmentosum can occasionally also affect the respiratory system in the form of an ILD. The underlying pathogenic mechanism behind this development is based on short telomere abnormality. This triggers an inflammatory state and precipitates ILD in such individuals on exposure to infection or hypersensitivity.[19] Patients diagnosed with ILD usually have symptoms of cough or dyspnea on exertion; for many, there is evidence of pulmonary restriction, decreased diffusion capacity, and radiographic appearance of alveolar and/or reticulonodular infiltrates.[20] The onset of respiratory symptoms can be in childhood or they could be noticed in early adulthood like in our case. The XPILD is peculiar in its histology, which is uniquely characterized by chronic inflammation and lung fibrosis. In our case, as the patient is very symptomatic, TBLB was not done and as signs and symptoms are non-specific, the clinical examination usually does not contribute to the diagnosis of ILD. On pulmonary function testing, restrictive lung disease may express the presence of an interstitial process. In our patient, pulmonary function test showed a restrictive pattern with FVC of 9% and IP of 10%. Knowledge of its existence is pertinent to maintain a high index of suspicion for unearthing its diagnosis in such rare syndromes. This helps to attain a definitive diagnosis by a multidisciplinary approach and avoid unnecessary invasive investigations like a lung biopsy.

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